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Friday
November 7, 1980

Part II

Department of Health and Human Services

Food and Drug Administration, Public Health Service and Health Care Financing Administration

Alpha-Fetoprotein Test Kits; Proposed Restrictions and Proposed Additional Quality Control and Testing Requirements

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 16, 20, 899

[Docket No. 80N-0002]

Alpha-Fetoprotein Test Kits

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing, for public comment, regulations to restrict the sale, use, and distribution of alpha-fetoprotein (AFP) test kits. AFP test kits are used in prenatal detection of a class of birth defects known as neural tube defects (NTD's). A public hearing will be held on the proposed regulations. Elsewhere in this issue of the **Federal Register**, the Centers for Disease Control (CDC) and the Health Care Financing Administration (HCFA) are proposing additional quality control and testing requirements applicable to laboratories engaged in AFP testing.

DATES: Comments on or before January 6, 1981. Public hearing on January 15, 1981; notices of participation by December 8, 1980; applications of public hearing participants for reimbursement by November 28, 1980. FDA intends that the final regulations will be effective 60 days after the date of publication of the final rule and will expire 4 years after first approval of an AFP test kit.

ADDRESS: Written comments, notices of participation, and applications for reimbursement to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Joseph M. Sheehan, Bureau of Medical Devices (HFK-70), Food and Drug Administration, 8757 Georgia Ave., Silver Spring, MD 20910, 301-427-7114.

SUPPLEMENTARY INFORMATION:

I. Background

Neural tube defects (NTD's) are among the most common serious birth defects in the United States. About 5,000 of the 3 million babies born each year in the United States have NTD's, an incidence of between 1 and 2 per 1,000 births. NTD's result when the neural tube, the developmental structure from which the spinal cord and brain of the fetus form, does not close properly during the early development of the fetus. About half the NTD's are characterized by a missing or malformed cranial vault or brain (anencephaly). There are roughly the same number of cases of spina bifida, in which the spinal column is open or otherwise fails to develop properly. Almost all infants affected by anencephaly are stillborn or die shortly after birth. The health of patients with spina bifida is often significantly impaired by conditions including paralysis of the lower limbs, mental retardation, incontinence, recurrent urinary infections, and hydrocephalus (excessive cranial fluid).

The cause of NTD's is not known. Only about 5 percent of affected babies are born to couples who have a family history of NTD's; about 95 percent of the cases are born to couples with no known risk factors (Ref. 1). Geographic variations in incidence both within the United States and internationally have been reported (Ref. 2). The rate of NTD's in the United Kingdom, for example, is about three times that of the United States. NTD's occur twice as often among whites as blacks in the United States, and in certain parts of the country—notably, Appalachia—the incidence of NTD's is well above the overall incidence in the United States.

An AFP determination together with confirmatory diagnostic procedures can alert parents and physicians to the possibility of an NTD fetus. AFP is a protein produced by the developing fetus. Its function has not been determined, though there is some indication that it is involved in regulating the fetal immunological system. AFP appears in the amniotic fluid surrounding the fetus at increasing levels during the first 14 weeks of pregnancy, after which the level usually declines. Since 1972, investigators have noted abnormally high levels of AFP in the amniotic fluid of fetuses with open NTD's (Ref. 3). Anencephaly is an open NTD; about 85 percent of spina bifidas are open lesions. Fetuses with anencephaly and spina bifida apparently shed an increased amount of AFP, which accounts for a higher than expected amniotic fluid AFP level for a given gestational age. Closed lesions generally are not detected by measurement of AFP levels.

AFP is also found in the mother's blood, perhaps due to direct transfer across the placental barrier or to the AFP in the amniotic fluid crossing the fetal membranes. AFP levels in the maternal blood increase during pregnancy, reaching a maximum at 32 to 34 weeks. An elevated maternal serum AFP level can be an indirect indication of the possibility of an NTD in the fetus. However, it may also be due to other factors, such as multiple fetuses, e.g., twins, or intrauterine fetal death. Investigators have also noted raised AFP levels in women bearing children with other congenital defects (Ref. 4); women with elevated AFP blood levels have been reported to be at greater risk of spontaneous abortion, perinatal deaths, and other pregnancy complications (Refs. 3 and 5).

An elevated maternal serum AFP level, therefore, is not diagnostic for NTD's. Accordingly, the AFP test kits are usually used in conjunction with other procedures to detect NTD's. The protocol generally followed includes the following steps, although the sequence may vary:

1. The serum AFP test is performed between 15 and 22 weeks of gestation.
2. If the first serum AFP is elevated, a second serum test is usually performed.
3. If the second serum AFP level is elevated, ultrasonography (diagnostic ultrasound) is used to determine whether the test results can be explained by incorrect estimate of gestational age, multiple fetuses, or fetal death. Anencephalic fetuses can often be identified at this stage.
4. If the elevated AFP level remains unexplained, amniocentesis is performed before the 22d week of gestation and amniotic fluid AFP levels are measured.
5. If fetal blood is present and the AFP level is elevated, amniocentesis is repeated 7 to 10 days later. Fetal blood can contaminate the amniotic fluid and cause a false-positive test result.
6. If the AFP levels in the fluid remain elevated, the physician may conduct additional studies, such as amniography or more extensive ultrasonography, to confirm or rule out suspected NTD's. Biochemical tests for analytes involved in neural transmission and morphological analysis of amniotic fluid cells in short term cultures are research procedures currently being studied to enhance the reliability of NTD detection by the examination of amniotic fluid AFP levels. Measurements of acetylcholinesterase in amniotic fluid have also been used.
7. Information and counseling are provided to the patient throughout the testing to enable her to make informed choices about whether to proceed with the testing, how to interpret the results, and to understand options available to her.

Of the steps listed, an elevated amniotic fluid AFP level following an elevated maternal serum AFP test is currently the most reliable diagnostic indicator of an NTD given a normal sonogram (to establish fetal age, a single fetus, and the absence of anencephaly). Amniotic fluid is obtained, however, by means of amniocentesis, an invasive procedure that carries a small risk of

fetal death. The AFP blood test can be used to help screen out those pregnant women who are at high risk of carrying an affected baby, and for whom amniocentesis may be justified.

The analysis of amniotic fluid is not fully accurate, however. The proportion of women who will have elevated amniotic fluid AFP levels and be carrying a child without an NTD is probably about one in ten (Refs. 3, 11, and 12). (In some of these cases, the fetus may have a defect other than an NTD.) Subsequent tests, such as amniography and an extensive ultrasound examination, can further reduce the likelihood of misdiagnosis.

Interest in AFP testing of pregnant women is increasing both in the United States and abroad. A number of testing programs have been established in the United States for the purpose of diagnosing NTD's. In addition, AFP tests are sometimes conducted on the amniotic fluid of (1) women undergoing amniocentesis for indications other than high risk for an NTD; and (2) women who have previously given birth to an NTD baby.

The United Kingdom has been in the forefront of AFP testing and research. A number of local health centers of the National Health Service provide maternal serum screening; an extensive quality control program has been established; and test outcomes have been widely studies.

In 1977 and 1979, published results on a collaborative study of 19 centers doing AFP testing in the United Kingdom documented the effectiveness of AFP testing in the detection of NTD's and provided a framework for laboratory and clinical procedures (Refs. 7 and 8). The United Kingdom established a government commission that explored and recently reported on the feasibility of a national screening program (Ref. 10a). In France, a serum screening is done only in state hospitals (Ref. 9); Finland has a state-operated pilot screening program in two parts of the country; it serves annually about 5,000 of Finland's 70,000 pregnant women (Ref. 10).

In addition, AFP test kits have been marketed for the past several years in Canada, Japan, and some European countries for screening for germ cell tumors and to monitor the progress of patients in remission from germ cell tumors. In the People's Republic of China, AFP tests have been used extensively to screen for malignant hepatomas.

Because AFP test kits for measuring AFP in maternal serum or amniotic fluid for the detection of NTD's were not commercially marketed in the United States before the enactment date of the Medical Device Amendments of 1976 (see 44 FR 11832; March 2, 1979), these devices are classified as class III devices under section 513(f)(1) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360c(f)(1)). Class III devices must be approved by FDA prior to marketing (section 515a (21 U.S.C. 360e(a))); see also section 513(a)(1)(C) (21 U.S.C. 360c(a)(1)(C)). FDA has denied a petition by Abbott Laboratories to reclassify this product, under section 513(f) of the act (21 U.S.C. 360c(f)), into class II (standards) (see 44 FR 11832).

FDA has received several applications under section 515(c) of the act (21 U.S.C. 360e(c)) for premarket approval (PMA) of radioimmunoassay test kits to measure AFP as an aid to detect NTD's. In the **Federal Register** of August 3, 1979 (44 FR 45644), FDA published a notice of its intent to issue proposed regulations under section 520(a) of the act (21 U.S.C. 360j(e)) establishing restrictions on the sale, distribution, and use of AFP test kits as a condition of approval of any such applications. FDA has decided not to approve any applications for premarket approval of AFP test kits as an aid to detect NTD's until it has determined through this rulemaking process what restrictions, if any, are needed to assure the safety and effectiveness of the kits. Manufacturers may not distribute AFP test kits in the United States for investigational purposes in accordance with the FDA investigational device exemption (IDE) regulations (21 CFR Part 812). Firms that have submitted PMA's to FDA for AFP test kits before July 16, 1980 (the effective date of the IDE regulations), are considered to have in effect an approved IDE.

On February 26, 1979, FDA held a public hearing on AFP test kits before two of its advisory committees, the Obstetrics-Gynecology Device Section of the Obstetrics-Gynecology and Radiologic Devices Panel and the Immunology Device Section of the Immunology and Microbiology Devices Panel. Summary minutes of the Panel meetings are on file in the office of the FDA Hearing Clerk.

FDA and the National Center for Health Care Technology (NCHCT), in collaboration with the National Institutes of Health (NIH), the Centers for Disease Control (CDC), and the Health Services Administration (HSA) (all components of the Department of Health and Human Services (HHS)) held a national education symposium on maternal serum AFP on July 28–30, 1980, in Washington, DC. The proceedings of this symposium will be made part of the administrative record for this proposal when available.

II. Is There a Need for Restrictions?

Section 515(d) of the act requires approval of AFP test kits upon a showing that they are "safe and effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling." That section further provides that the approval may be subject to such conditions as FDA may prescribe:

> If, because of its potentiality for harmful effect or the collateral measures necessary to (their) use, (FDA) determines that there cannot otherwise be reasonable assurance of (their) safety and effectiveness.

(Section 520(e)(1).)

Several health professional and consumer organizations, as well as specialists in AFP testing, have told FDA that although they recognize that the AFP test is beneficial, they fear that unrestricted use of the AFP test kits could increase the chance of the serious complications, e.g., abortion of normal fetuses, failure to identify affected fetuses, and prospective parents' becoming unnecessarily alarmed about the outcome of the women's pregnancy (Ref. 13–24). Others have expressed the view that the AFP test kits are safe and effective and should be made available as widely as possible, to give women who may be carrying NTD fetuses the greatest possible access to this technology for identifying them (Refs. 41 and 42).

These potentially conflicting concerns have created a dilemma for FDA in deciding the conditions under which AFP test kits can be used safely and effectively. FDA believes any restrictions must take into account both the goal of appropriate access to this useful test and the need for assurance that the entire set of test procedures is available to any woman who undergoes AFP testing. FDA has considered various alternatives (which are described later) for meeting those requirements and decided to propose in regulatory language an approach which emphasizes use of the test under controlled conditions. FDA believes this approach best raises the difficult issues concerning AFP tests for public consideration and gives the public notice of the range of restrictions that could be imposed. FDA is proposing regulations which, if adopted, would require that AFP test kits be used only as part of a program in which a coordinator certifies in writing to FDA that an array of specified services would be provided to patients. These services

would include laboratory testing, ultrasonography, amniocentesis, and counseling. The regulations would also prescribe, in considerable detail, requirements for the laboratories and other service providers, and would require detailed recordkeeping. In addition, manufacturers would be required to provide comprehensive information to physicians, laboratories, and patients. FDA emphasizes, however that the scheme set out in this notice is only a proposal. FDA hopes by this notice to stimulate a broad range of discussion among affected interests and the general public before developing a final rule.

Each of the proposed restrictions is described below, together with many questions about particular provisions, there are more general issues on which public comment is especially invited:

(1) As with screening tests in general, AFP kits are not 100 percent specific. Thus, of 1,000 pregnant women whose blood is tested with an AFP kit, about 50 will have elevated AFP levels. A second blood test will reduce that number to about 30, sonography to about 15, and amniotic fluid AFP testing to about 2. Moreover, of 10 women who manifest elevated AFP levels in amniotic fluid, 1 will be carrying a normal child.

Thus, AFP testing presents in microcosm a problem frequently encountered with diagnostics: It can considerably improve the physician's and patient's knowledge of the situation, but it is not perfect. The error can occur in either direction. That is, an AFP test may predict that the fetus has an NTD when, in fact, it does not—a false-positive; or it may predict that the fetus does not have an NTD when, in fact, it does—a false-negative. If confirmatory procedures are available to reduce the error rate, as they are here, what is the best means of ensuring that patients and physicians are aware of the need for doing the confirmation procedures? Should FDA require that these confirmation procedures be conducted or at least made available to the patient?

What role should patient autonomy play in this decision? That is, once a technology is available which can give a patient some information, why and when should that information be denied her or him merely because the information is not perfect?

a. Excessive restrictions on AFP testing may discourage physicians, laboratories and patients from engaging in AFP testing. To the extent that the restrictions limit access to AFP testing, many women will not be tested and, therefore, will not have the information upon which to base decisions on the future of the pregnancy. How should the balance be struck between restrictions on use of the kits and the widest possible patient access to the technology? Is widespread access desirable?

b. Under the proposed restrictions, AFP testing may be available for the most part at medical centers capable of providing under one roof—or at least within a relatively small geographical area—all the necessary services. How would physicians gain access to program participation if there were no program in their areas? Or there is a program in the area, but the coordinator does not allow a particular physician to participate? Would the proposed restrictions unfairly deny women in certain geographic areas or of limited income access to AFP testing?

(2) AFP test kits have been under active review by FDA for several years. Much of the concern expressed about their unrestricted use came in the earlier part of that time. In the interim, have increased experience with AFP test kits and greater familiarity with them by the medical profession reduced the need for restrictions on their distribution?

(3) One manufacturer has estimated that the proposed restrictions would increase the costs of a test kit by 50 percent, e.g., from $150 to $225 for a kit that can be used for 40 patients. Are these figures accurate? Are the additional costs that the proposed restrictions would impose on consumers justified by the benefits?

(4) Are there sufficient resources in this country to provide the ancillary services required for AFP testing? If not, will the existing capacity for delivery of these services expand as necessary in response to demand? Even if the capacity might not expand as necessary, should FDA nevertheless approve AFP test kits so that at least some women will benefit from AFP testing?

III. The Proposed Restrictions

1. *Diagnostic protocol.* The regulations in effect establish a preferred diagnostic protocol. Should alternative protocols be suggested as well? Measurement of acetylcholinesterase in amniotic fluid, for example, has been suggested as useful in the diagnosis of NTD's in pregnancies with positive amniotic fluid AFP results (Ref. 12a). Has the development of the acetylcholinesterase test reached the stage that it should routinely be used in the diagnostic protocol? Would the use of the acetylcholinesterase test diminish the need for quality ultrasound to confirm the presence of an NTD?

2. *The coordinator.* The proposed regulation would require a program to have a coordinator who provides a written assurance to FDA that the program will comply with FDA regulations on AFP testing. The coordinator would oversee the timely delivery and quality of needed followup services. The coordinator may, for example, be the director of an existing genetics program or an individual responsible for a program established specifically for AFP testing.

To qualify as a coordinator under the proposed regulations, an individual would submit a letter containing his or her name, address, and telephone number, and the certification that is described in proposed § 899.82(a). That certification states that certain requirements FDA considers essential for an AFP testing program have been met. Proposed § 899.82(b) provides that when FDA receives a letter from the coordinator containing the certification required by the regulations, FDA would provide the coordinator with an enrollment number. The coordinator would then provide this number to physicians and laboratories that are part of the coordinator's program.

One proposed requirements is that the program have within its organization, or obtain through written agreements with other providers, access to services, for example, amniocentesis, ultrasonography, and laboratory services, enabling the program to offer patients all procedures necessary for proper diagnostic followup. FDA is proposing the requirement in the belief that it may not be enough for the coordinator merely to locate a facility providing the services. As proposed, the coordinator would be required to have written agreements for patients in the program to use that facility. Any written agreement would have to establish that the provider of the service would agree to provide services to patients within the AFP testing program and would comply with applicable provisions of the proposed regulations.

Are people available to fill the role of coordinator? Who would pay them? What would they cost? What are the incentives and disincentives to volunteer as a coordinator?

Are coordinators essential to assure the timely delivery of ancillary and confirmatory services for AFP testing? Is a prearranged program the only means of assuring the availability and timely delivery of services? Are there other, more appropriate, mechanisms available? Are there parallels between AFP testing and other diagnostic procedures which suggest alternative mechanisms?

3. *Ultrasonography.* Ultrasonography may be used several times in the course

of screening for NTD's. First, an ultrasound examination is conducted to estimate gestational age because AFP values can be correctly interpreted only in relation to the age of the fetus. Ultrasonography should also be able to rule out multiple fetuses, fetal death, and to identify anencephalic fetuses. If these alternate explanations for elevated AFP serum levels cannot be ruled out, either because ultrasound is unavailable or because it is not of adequate quality, some women will be unnecessarily exposed to risks, costs, and anxieties associated with subsequent procedures. Clinical trials suggest that close to half of all women with elevated serum readings might be spared further testing by effective use of ultrasound before amniocentesis.

Ultrasonography is also used in conjunction with amniocentesis to locate the placenta and the fetus and to identify the best site for inserting the needle. More extensive ultrasound examinations may be used after a positive amniotic fluid AFP test to provide a detailed image of the fetus to attempt to locate a suspected defect. This latter examination is complex and time-consuming and requires additional expertise and, perhaps, more sophisticated equipment.

Proposed § 899.83(a)(2) would require that a competent diagnostic ultrasound service be available that is capable of identifying multiple fetuses and anencephaly, accurately determining gestational age and detecting fetal death. Such a facility would have to agree to comply with applicable provisions of the regulation.

The availability of equipment for ultrasonography early in the testing protocol does not appear to be a significant problem. In 1974, an FDA survey of 1,000 United States hospitals of various sizes indicated that there was sufficient ultrasound imaging instrumentation to provide ultrasound examinations for approximately one-third of the total pregnancies at these institutions (Ref. 26). The substantial growth rate of ultrasound since that time suggests that there is access to ultrasound facilities for obstetric applications. A limited 1979 survey reported in *Radiology/Nuclear Medicine Magazine* showed that ultrasound facilities are available in radiology or obstetric services at over 70 percent of the responding institutions (Ref. 27).

Although ultrasonography may be widely available, FDA is concerned that all patients have access to services of sufficiently high quality for use in AFP testing. FDA welcomes comment on the degree of expertise needed to do AFP testing and the availability of that level of expertise. In addition, it would be useful to know how much training and experience is needed to reach that level of expertise. FDA has received comments from the Society of Obstetric and Gynecologic Ultrasound (SOGU) stating that "the technology continues to outpace user experience" (Ref. 28). The Public Citizen Health Research Group (HRG), citing SOGU's discussion of limited training in ultrasonography and quoting other sources, concludes that "the present inadequacy of expertise in ultrasound and the unlikelihood of significant expansion of expertise in the near future should preclude, at present, the setting up of neural tube defect screening programs except on a limited, tightly controlled basis with firm quality control assurances for all components of the screening program" (Ref. 29).

Training and experience for both technologists and physicians has been discussed in the professional literature (Refs. 30 through 33). Education and certification guidelines for technologists have recently been recognized by the American Medical Association's Committee on Allied Health Education and Accrediation. Some questions about ultrasound are now included in the Board Examinations in Obstetrics and Radiology.

The Commission on Ultrasound of the American College of Radiology (ACR) has recommended that: (1) Residents in radiology receive a minimum of 3 months training in ultrasound; (2) radiologists wanting a career in ultrasound seek a fellowship of a minimum of 1 year; and (3) practicing radiologists just starting in ultrasound receive a minimum of 1 month of formal training in ultrasound technique and interpretation before using the modality (Refs. 39 and 40).

SOGU has recommended that the equivalent of 2 months out of a 4-year postgraduate residency training course in obstetrics and gynecology be devoted to interpretation and supervised performance of both static and real-time B-scan ultrasound examinations.

Under proposed § 899.83(a)(2), competent diagnostic ultrasound service would require ultrasound equipment and competent physicians to interpret ultrasound scans. There are currently no uniform ultrasound training criteria. Therefore, FDA has not attempted to define "sufficient" training and experience. Should it? Would program coordinators be able to determine that ultrasound services are of sufficiently high quality? Is the coordinator in a better position to make this determination than the patient's own physician?

4. *Amniocentesis.* Proposed § 899.83(a)(3) would require that amniocentesis for the purpose of obtaining amniotic fluid to measure AFP levels be available to all women in the testing program who require it. The proposal requires the coordinator to assure that the program has available facilities to draw the amniotic fluid and to analyze that fluid for AFP, and that these facilities agree to comply with applicable provisions of the regulations. This requirement is intended to reduce the possibility that a woman with elevated maternal serum AFP would not have access to the diagnostic AFP amniotic fluid test.

HSA has told FDA that it believes resources are inadequate to meet the demand if AFP screening were undertaken as a routine procedure (Ref. 34).

Amniocentesis may be done in a physician's office, a hospital, or at a tertiary genetics center (a facility usually affiliated with a major medical center that offers a wide range of genetic services).

The procedure is done in either the second or third trimester of pregnancy, depending on the reason for the test. It is usually performed in the second trimester for chromosomal analyses of cells in amniotic fluid of women who, because of advanced maternal age or other reasons, are at increased risk of bearing a child with a birth defect.

FDA is not aware of any complete source of data on the total number of second trimester amniocenteses performed in the United States each year. The report of the NIH Consensus Development Conference, published in April 1979, however, estimates on the basis of surveys and regional data that about 15,000 second trimester procedures were performed in the country in the preceding year (Ref. 20).

FDA cannot predict exactly how widespread and how rapid adoption of AFP testing will be. FDA believes, however, that approval of the AFP test kit would generate a significant increase in the number of amniocentesis procedures being performed.

Of the women who have the first serum AFP test, approximately 2 percent will need to have access to second trimester amniocentesis. If all pregnant women were tested, an additional 60,000 amniocentesis procedures could be generated each year. Not all pregnant women, however, receive prenatal care in time to benefit from AFP testing. Furthermore, some women or physicians can be expected not to participate. It is unlikely, therefore, that there will be a demand for the maximum number of 60,000 additional amniocenteses. Taking

into account likely participation in a national NTD screening program, Goldberg and Oakley have projected that approximately 28,000 amniocenteses annually would be generated in a national screening program (Ref. 2). this figure does not include possible repeat amniocenteses, for example, where fetal blood contaminates the first sample and the test is positive, or where the test result is borderline.

Would the suply of amniocentesis services be adequate to meet the demand caused by increased AFP testing? If not, how quickly could the supply be increased?

5. *Counseling.* Proposed § 899.83(a)(4) would require that counseling be available to all women who are considering being tested or who are participating in the testing. Under the proposal, the program coordinator must ensure that as part of the program there would be qualified personnel to discuss several issues relating to AFP testing and NTD's including: The procedures that may be performed as part of the testing; the risks and benefits of the testing; the likelihood of false-positive and false-negative test results; the significance of the test results; the range of severity of NTD's; and options available to the patient with abnormal diagnostic test results. The counseling services should be based on a policy of voluntarism about the options of a patient with abnormal test results, especially with respect to the choice of termination of pregnancy.

Should it be left open whether counseling should be done by the physician, nurses, other health care professionals, or specially trained laypersons; or should genetics counseling be provided by qualified counselors? Should access to counseling be left to the patient's individual physician? Or must the program coordinator perform that function? Who would pay the counselors? What would they cost?

The American College of Obstetricians and Gynecologists (ACOG) has told FDA that the level of expertise and numbers of trained counselors necessary to deal with the patient's anxiety are "insufficient" to handle the need for counseling that would be associated with unrestricted use of AFP test kits (Ref. 36). Historically, has the availability of counselors to consult with patients about birth defects increased in rough proportion to the demand so that government intenvention to assure the availability of counseling is unnecessary?

FDA invites comment on whether patient anxiety would in fact occur, and if so, whether it would be any greater than, or different from, anxiety patients now manifest about other possible birth defects. Are comparably comprehensive counseling systems for other potential problems such as Down's Syndrome available? Could such existing systems be adapted to serve women ungoing AFP testing? Would the availability of appropriate printed patient information, together with interpretative aid from the patient's physician, family, or others, be sufficient?

6. *Laboratories.* Proposed § 899.85(a) would require that a laboratory be part of a program enrolled with FDA to purchase AFP test kits for use in NTD testing. A laboratory would prove that it is part of a program by providing the enrollment number of the program to the manufacturer.

Proposed § 899.85(b) would provide that laboratories may accept samples for AFP tests only from physicians who are part of a program enrolled with FDA. All samples would have to be accompanied by the FDA enrollment number.

Proposed § 899.85(c) would require that laboratories doing AFP testing follow the manufacturer's approved labeling unless alternative procedures are justifiable. The labeling would specify that each laboratory must establish its own normal median values for serum and amniotic fluid for each manufacturer's test kit used by the laboratory. The normal median values would have to be independently established for each manufacturer's AFP test used by each qualifying laboratory for each appropriate gestational week (that is, the 15th to 22d gestational weeks) from a statistical basis that includes maternal sera or amniotic fluids obtained from at least 100 screened women, each with a singleton conceptus that is unaffected by NTD's.

While normal median values are being established in a laboratory, that laboratory would be permitted to provide AFP test results to a physician, using, as a guide for interpretation, normal values obtained from the manufacturer of the AFP test kit used by the laboratory. Any abnormal AFP values during this period, however, would be required to be confirmed by repeat analysis of the same sample at a laboratory with an established range of normal values using the same manufacturer's approved AFP test kit. FDA believes that verifying results in this way would adequately ensure that analysis of samples by laboratories that have not yet developed normal AFP values would not lead to inaccurate reporting of normal samples as containing elevated AFP levels.

Laboratory labeling for each manufacturer's test kit would include summaries or explanations of the following: (1) AFP measurement procedures; (2) the protocol for AFP assay; (3) the principles of radioimmunoassay procedure; (4) the reagents and their preparation; (5) indications of instability; (6) radioactivity warnings; (7) specimen collection and preparation; (8) sample preparation; (9) the procedure for testing; (10) results of data accumulation; (11) a description of cutoff levels; (12) limitations of the procedure; (13) expected values; (14) performance characteristics; (15) the protocol and flow charts for AFP and associated modality testing; (16) the standard curve preparation calculations and quality control procedures; and (17) summary tables of maternal serum and amniotic fluid values obtained in clinical studies. The physician would send a manufacturer-supplied tear-off sheet to the laboratory with each sample to be tested; the laboratory would return the tear-off sheet to the physician along with the test results; it would include the median values and multiples of the median for gestational weeks 15 to 22 and a description of the need for followup procedures if the test result is positive.

To facilitate statistical comparison of normative and cutoff data obtained with different manufacturers' AFP test kits, each manufacturer would be required to calibrate its AFP test kit against the World Health Organization Reference Standard for Human Alpha-Fetoprotein (72/225) and report, in its professional and laboratory labeling, the mass of AFP found by use of its AFP test kit that is equivalent to one International Unit of AFP.

Under proposed § 899.85(d), the laboratory would be required to participate successfully on a regular basis in an FDA endorsed proficiency survey. Generally, proficiency testing programs are designed to monitor a particular laboratory's performance by comparing its quantitative results to those obtained by reference laboratories. FDA is working with CDC on a proficiency testing program for AFP. The College of American Pathologists (CAP) has informed FDA that it will be establishing a proficiency testing program shortly. The Commission on Inspection and Accreditation of the CAP is one of several national accreditation bodies approved by the Secretary, HHS, for accrediting laboratories under 42 U.S.C.

263a. (See § 74.1(e) of CDC's clinical laboratories regulations (42 CFR 74.1(e))). Proposed § 899.85(d) would require laboratory participation in either CDC's or CAP's proficiency testing programs or any other one subsequently endorsed by FDA.

As with other facilities participating in the program, proposed § 899.85(d) would require any laboratory that wishes to obtain AFP test kits for NTD testing to agree to participate in an inspection program authorized by FDA. Inspections would be made on a surveillance basis or for-cause to assure compliance with the regulations. HCFA would share responsibility for laboratory inspections with FDA, and both agencies are currently working to develop a Memorandum of Understanding to avoid duplicative inspections. The records the laboratory would be required to keep for inspectors to assure compliance are set out in proposed § 899.85 (f) through (h).

Proposed § 899.85(i) would require a participating laboratory to report test results greater than 2.5x the median to the program coordinator as well as to the attending physician. Because of the need for rapid followup testing, FDA believes that it is desirable that the laboratory telephone the results while the written report is being delivered. The laboratory would make data on AFP testing available to the coordinator, as requested, for submission in the manufacturer's reports so that coordinators may monitor the program.

A joint task force of ACOG and the American Academy of Pediatrics (AAP), HRG, CDC, and two NIH conferences on AFP (Refs. 20 and 37) have recommended that AFP testing be restricted to laboratories that conduct what they consider to be an adequate volume of AFP tests. The NIH workshop report (Ref. 37) suggested 50 maternal sera AFP samples and 10 amniotic fluid samples weekly. The ACOG/AAP report (Ref. 22) suggested 100 maternal sera tests weekly. CDC has proposed a minimum weekly sample workload of 50 mid-pregnancy patient specimens as regulatory requirements. The CAP does not favor minimum volume or frequency requirements on the grounds that they are not necessary to ensure proficiency. CDC asserts that there are statistics on several assays that indicate that laboratories routinely testing only a few samples each week have a much larger number of unacceptable results than do laboratories with a larger workload. CDC also points out that some State regulations prohibit laboratories from offering certain types of tests unless the laboratories perform tests of samples at a fixed workload and frequency.

After consultation with CDC, FDA has decided that it would be appropriate to propose at this time that, within 1 year after enrollment in the program, a laboratory be required to test a minimum total of 50 of any combination of maternal serum and amniotic fluid samples each week and proposed § 899.85(e) so provides. A CDC/HCFA joint proposal, published elsewhere in this issue of the **Federal Register**, would require the same weekly sample workload for clinical laboratories licensed by CDC to conduct AFP testing, and to be reimbursed by HCFA under the medicare program. Are these requirements necessary to assure the quality of laboratory performance? Any comments dealing with volume or assay frequency should, if possible, cite data or other pertinent supporting information.

7. Reporting requirements. Proposed § 899.84(c) would require manufacturers of AFP test kits also to submit quarterly and annual reports to FDA summarizing the results of AFP testing at each program. Quarterly reports would enable FDA to determine the abnormal/normal fetus abortion ratio at the individual programs. The proposed annual reports would include more detailed data to rates associated with each manufacturer's AFP test kit. FDA will specify the content and timing of submissions in the premarket approval orders to individual manufacturers.

Proposed § 899.83(d) would require the coordinator to secure written agreement from each physician involved in the program to notify the coordinator of the pregnancy outcome in all cases with an elevated AFP level and of all pregnancies involving fetuses with an NTD. All facilities associated with the program would also report abnormal test results to the coordinator, as well as to the attending physician. These data would enable the coordinator to monitor the performance of the program. They would also form a part of the data submission that proposed § 899.83(e) requires the coordinator to provide to the manufacturer of each kit used by that program.

FDA proposes that each coordinator would be required to furnish the current data FDA requires as part of the approval of a premarket approval application for an AFP test kit to the manufacturer of any AFP test kit used by a laboratory within the coordinator's program 15 days before the manufacturer must submit its quarterly report. FDA also proposes that, for any pateint undergoing amniocentesis to enable the measurement of AFP in amniotic fluid, the coordinator be required to furnish the manufacturer the information required by § 899.83(g) within 35 days of amniocentesis. The data would, in turn, be used by the manufacturers for quarterly and annual reports to FDA.

FDA intends to make available to the public, on a regular basis, summary analyses of the data it receives as part of the program, and to include in these summaries as much relevant information as is permissible under sections 301(j) and 520(c) of the act (21 U.S.C 331(j) and 360j(c)), the Trade Secrets Act (18 U.S.C. 1905), the Freedom of Information Act (5 U.S.C. 552), and the Privacy Act of 1974 (5 U.S.C. 552a). For example, these summaries will include data identified by the manufacturer. The data will not be retrievable by the name of the individual patient, and there will be no other means of identifying an individual patient. Thus the Privacy Act of 1974 does not prohibit the public disclosure of these data (see 5 U.S.C. 552a(a)(5)). FDA has determined that this information does not constitute trade secret information.

In addition to the postmarketing data requirements described above, CDC intends to conduct an epidemiological study to obtain additional information on AFP testing and NTD's. FDA will cooperate with CDC in this effort.

For inspectors authorized by FDA to determine whether a program is in compliance, the proposal would require coordinators, manufacturers, physicians, and facilities associated with the program to keep certain records. These are set out in appropriate sections of the regulations.

Proposed § 899.83(g) describes the records the coordinator would be required to keep. These records would enable authorized inspectors to identify facilities and physicians used by patients associated with the program who test abnormal or whose pregnancies involve an NTD fetus. The records would also be used to verify data submitted in the manufacturers' quarterly and annual reports and to identify facilities or circumstances which may require further followup investigation.

To verify distribution of test kits to approved programs, proposed § 899.84(d) would require manufacturers to maintain distribution records for AFP test kits.

Authorized inspectors must also be able to inspect raw data generated by facilities within the program as part of the AFP testing. Proposed §§ 899.85(f) and 899.87(a) respectively, therefore, would require the laboratory and the ultrasound and amniocentesis facilities

either to maintain specified records or to identify the location of such records. FDA does not anticipate that these proposed recordkeeping requirements would create an undue burden on the facilities because the records are those that would typically be generated in the delivery of services.

As proposed, physicians participating in an enrolled AFP testing program would be required to maintain records for each patient involved in AFP testing as described in proposed § 899.86(e). These records could be inspected to verify information supplied to the coordinator. FDA believes that this proposed required recordkeeping is typical of patient records a physician would keep and, therefore, should not create an undue burden on the physician. Further, FDA would not expect to inspect physicians' offices on a routine basis. Rather, it generally would expect to examine records in participating physicians' offices, including those ultrasound and amniocentesis facilities which are physicians' offices, only on a "for cause" basis.

Proposed § 899.89 would provide that program records must be maintained for 2 years following the expiration of the final regulations to permit FDA to conduct any necessary followup investigations and to verify the manufacturers' data submissions.

The recordkeeping and periodic reporting requirements contained in this proposal are subject to clearance by the Office of Management and Budget (OMB) under the Federal Reports Act of 1942 (44 U.S.C. Chapter 35). FDA intends to submit to the Director, OMB, copies of this proposal and other related materials during the comment period on the proposal. If OMB approves the proposed requirements, FDA will include them, along with any changes resulting from comments, in the final regulations as necessary to comply with OMB's determination. FDA will, if appropriate, also make conforming changes in any recordkeeping and reporting requirements applied in premarket approval orders for individual AFP test kits. Any comments received from OMB will become part of the administrative record for this matter and will be placed on file for public review in the office of the Hearing Clerk, FDA, in Docket No. 80N–0002.

Are all of these recrodkeeping requirements necessary to the safe and effective use of AFP test kits? Would requiring the provision of information about abortions invade a patient's privacy, or deter her use of an AFP test? Are the costs of these requirements commensurate with their benefits?

8. *Physician education.* Proposed § 899.83(b) would require the program coordinator to ensure that all physicians in the program have a sufficient supply of professional labeling prepared by the manufacturer and approved by FDA. Professional labeling for each manufacturer's AFP test kit would include: (1) A description of the measurement of AFP as an indicator of NTD's; (2) the nature, incidence, and consequences of NTD's; (3) the AFP testing protocol, including the importance of adhering to time requirements and using confirmatory diagnostic procedures; (4) the significance of test results, including how to adjust interpretations for racial and geographic population int he United States; (5) the specificity and sensitivity of the tests; (6) expected values; (7) a description of the cutoff levels used to distinguish abnormal and normal values for the manufacturer's product; (8) the protocol and flow charts for AFP and associated modality testing; and (9) summary tables of maternal serum and amniotic fluid values obtained in clinical studies.

ACOG has emphasized to FDA its concern that physicians are not prepared to use the AFP test safely. ACOG also called for restricted distribution of AFP test kits and a major educational campaign for physicians to ensure that AFP screening for NTD's is fully understood before it is undertaken (Ref. 36).

Are the AFP test kits and confirmatory diagnostic procedures more difficult to understand or to undertake than diagnostic procedures now in use?

9. *Patient information.* Women must be aware of the risks as well as the benefits of AFP tests in order to make an informed decision about participating in the testing and taking actions on the basis of test results. Faced with test results indicating elevated AFP levels, women must be provided detailed information about the significance of the results and the likelihood that an elevated level signifies an affected fetus. A discussion of NTD's and the options available must also be provided to women at risk. General information could be provided to patients at an early stage of the testing; more detailed information at the later stages may also be helpful.

The Spina Bifida Association of America (SBAA), HRG, and the ACOG/AAP Task Force have emphasized the importance of patient education for safe and effective screening for NTD's (Refs. 16, 17, and 22). Without such information, women: (1) May not understand that further diagnostic tests may be necessary to confirm or rule out a diagnosis of NTD based on an elevated AFP level; (2) may not be aware of the time sensitivity of the initial tests and may report for tests or receive abnormal results too late to take action on the medical options; (3) may forego followup tests without understanding that these tests could relieve anxiety about the child; (4) may not know that many spina bifida children, with treatment, can lead productive lives; or (5) may fear that once they have an affected pregnancy they cannot bear normal children. These groups believe that patient information must address these issues. The following is a sample patient brochure on which FDA invites comment.

Patient Information for AFP Testing

This is about a new test called the alpha-fetoprotein (al-fah-fee-toe-pro-teen) (AFP) test. Doctors can use this test to help identify those pregnant women who may have an increased chance that their unborn baby has certain birth defects called neural tube defects (NTD's).

This leaflet will help you learn more about the AFP test and NTD's. If you are thinking of having this test you should read this leaflet and use it as you talk with your doctor.

What Are Neural Tube Defects?

In the early development of the unborn baby, the spinal cord and brain grow from a structure called the neural tube. As the unborn baby grows, this tube changes its shape, with the head region developing into the brain and the rest of the tube becoming the spinal cord. Together, the brain and the spinal cord make up the central nervous system. NTD's result when the neural tube does not completely close during the early development of the unborn baby.

What Are Some Types of Neural Tube Defects?

Two common and serious types of NTD's are *anencephaly* (an-en-sef-a-lee) and *spina bifida* (spy-nah biff-ah-da).

Anencephaly. In this disorder, much of the brain, head and spinal cord have not developed normally. Newborn children with this severe disorder usually die shortly after birth.

Spina bifida. This disorder is also called "open spine." It is a defect of the spine and nervous system. There are several forms of spina bifida.

(Illustration showing normal neural tube and varying degrees of severity of spina bifida.)

Children born with spina bifida are often handicapped in a number of ways.

In a few cases, normal development of the child with little physical handicap is possible. Often, however, paralysis of the lower limbs, repeated urinary tract infections, hydrocephalus ("water on the brain"), and mental retardation occur.

The spine malformation and nerve damage caused by this disorder hamper movement in varying degrees. Some individuals with spina bifida can walk by themselves. Others use braces and crutches or a wheelchair. Through modern surgical and corrective techniques, many children born with spina bifida can lead healthy and productive lives.

What Causes Neural Tube Defects?

The cause of neural tube defects is not known. It may be a genetic (inherited) defect, or it may be caused by environmental factors. The occurrence of this problem in the United States varies from region to region; neural tube defects seem to occur more often in areas which are highly populated. Much more research must be conducted to find out the cause of this problem.

What Are the Chances of a Baby Born With a Neural Tube Defect?

In the United States, about 1 to 2 live births per thousand involve a neural tube defect: About 3,000 to 6,000 of the three million annual babies. These birth defects are about equally split into the two main types: Anencephaly and spina bifida.

Of the 3,000 to 6,000 births that result in a neural tube defect, approximately 2,700 to 5,400 (90 percent) babies with such a defect will be born to women who have no special or common "risk" characteristic. The remaining 300 to 600 babies with neural tube defects will be born to women who have any one of the following "special risk" characteristics:

Women who have already given birth to a child with a neural tube defect; one or both parents have neural tube defects or; women whose mother or father has a history of neural tube defects.

Alpha-Fetoprotein Blood Test

What is Alpha-Fetoprotein (AFP)?

Alpha-fetoprotein is a substance that is produced by the unborn baby as it grows and is passed into the amniotic fluid around the unborn baby and then into the mother's blood.

When the neural tube is not properly formed, too much alpha-fetoprotein "leaks" into the amniotic fluid around the unborn baby and reaches the mother's blood. By measuring the amount of AFP in the mother's blood and amniotic fluid, it is possible to tell whether or not there is a *chance* that the unborn baby has a neural tube defect.

What is the AFP Blood Test?

A blood test is the first step that the doctor will take to determine whether or not an unborn baby may have a neural tube defect.

The AFP blood test is simple and does not present any significant risk to the mother or the unborn baby. The doctor will take a sample of blood from the vein in the mother's arm and send it to a laboratory. The laboratory will test the mother's blood to see how much AFP is present and then send the doctor the results of the test.

When Should a Pregnant Woman Have the AFP Blood Test?

The best time to have the AFP blood test is during the second trimester of pregnancy. The best time is 15–22 weeks after your last menstrual period. Unreliable results may be obtained if the blood sample is taken too early during the pregnancy. If the sample is taken too late, there may not be enough time to complete all the tests.

What Will the Test Results Mean?

If the mother's blood has normal levels of AFP, the test results will be considered negative and there will be no need for further tests. Approximately 950 out of 1,000 women who have this blood test will have a negative result.

It is important for parents to understand that an AFP blood test result in the normal range cannot guarantee a perfect baby at birth, but it can offer some reassurance that the baby will not have an open neural tube defect.

An elevated result indicates that there are high levels of AFP in the mother's blood. This does not always mean an NTD is present. It means that the woman requires more care and additional tests to see whether or not the unborn baby has an NTD. These additional tests are described later in this brochure. Approximately 50 out of 1,000 women who have the AFP blood test may have a positive result from the first blood test.

If a high AFP blood level is obtained, there is about a 2-in-100 (2 percent) chance that the unborn baby has an NTD. More likely reasons for the positive result are that the pregnancy is further advanced than you think, or that you are carrying twins.

A week after the first elevated blood sample, the doctor will take a second sample of blood from your arm. If the result of the second test is also elevated, there is about a 4 to 10-in-100 chance (4 to 10 percent) that your unborn baby has an NTD. At this time, the doctor will discuss the need for you to have additional tests that will give a more accurate diagnosis than blood tests.

Is There a Possibility of False Results?

Women who are thinking of having the AFP blood tests should be aware it is possible that NTD's may be missed by the test or that a healthy fetus may wrongly be identified as having an NTD. The possibility of these false results should be openly discussed by you and your doctor.

What Are the Other Tests That May Be Needed If the Second AFP Blood Test Is Elevated?

Sonography (so-nog-raf-fee). The first test is pulse echo sonography, in which high-frequency sound waves are used to obtain an image of the unborn baby. The results of this test can be used to tell whether the blood test was elevated because the woman is carrying twins, or because the week of pregnancy was estimated incorrectly. Sonography can also show if an unborn baby has died, and often whether an NTD is present.

Amniocentesis (*am*-nee-o-sen-*tee*-sis). In this test, the doctor will take a sample of the amniotic fluid around the unborn baby and send it to the laboratory to measure the AFP level in the fluid. If the AFP level is high and other possible causes (twins or the age of the fetus when the test was taken) have been ruled out, there may be a 19-in-20 (95 percent) chance or more that the unborn baby has a neural tube defect. This test cannot tell how bad the defect will be or the possible degree of the handicap.

If the amniotic fluid AFP is elevated, the physician may wish to attempt to visualize the possible defect by means of gray scale sonography (a more advanced and accurate type of ultrasound), or by amniography, in which the baby is outlined by radiopaque dye injected into the uterus.

The chart attached to this brochure shows for 1,000 pregnancies the estimated results from the full testing sequence on determining whether an unborn baby has an NTD.

What Are the Risks and Costs of the AFP Blood Test and Other Tests?

Women who receive two positive results from the AFP blood test should be aware that other tests are needed to be more sure whether the unborn baby has an NTD. The AFP blood tests carry little risks—no more than any other blood tests people can get. In addition, these blood tests do not cost too much to have done. If the blood tests are elevated, the other tests described above (sonography and amniocentesis) may present a small risk, and can cost more money. It is not known whether

sonography carries any risk. You should ask your doctor about these tests; the risks that they present; how much they cost; where these tests are given; and any other questions that may be of concern to you.

What Should You Do if the Tests Show That Your Unborn Baby Has a Neural Tube Defect?

Counseling can help parents to assess the choices they have in relation to their own personal capabilities, needs, and desires. Women should ask their doctor for information about counseling.

Estimated Results of AFP Testing Program

Number of pregnant women tested		1,000
Elevated result—1st serum sample		50
Elevated result—2nd serum sample		30
Referred for sonography		30
Twins	8	
Corrected gestational age	6	
Fetal death	1	
Unexplained elevated serum AFP	15	
Referred for amniocentesis		15
Normal AFP	13	
unexplained elevated amniotic fluid AFP	2	
Referred for amniography or gray scale sonography		2
Normal	1	
NTD	1	

FDA invites comments on the brochure, particularly in the form of suggested alternative language to make the brochure more understandable and to add or delete information.

10. *Patient acknowledgment.* Under proposed § 899.86(a) a physician in the program would be required to obtain from each patient written acknowledgment that she: (1) Has been provided with the patient brochure prior to receiving the first AFP test, (2) has had an opportunity to discuss questions related to AFP testing with the physician or a counselor familiar with the subject, and (3) authorizes government employees to review and if necessary copy her records related to AFP testing.

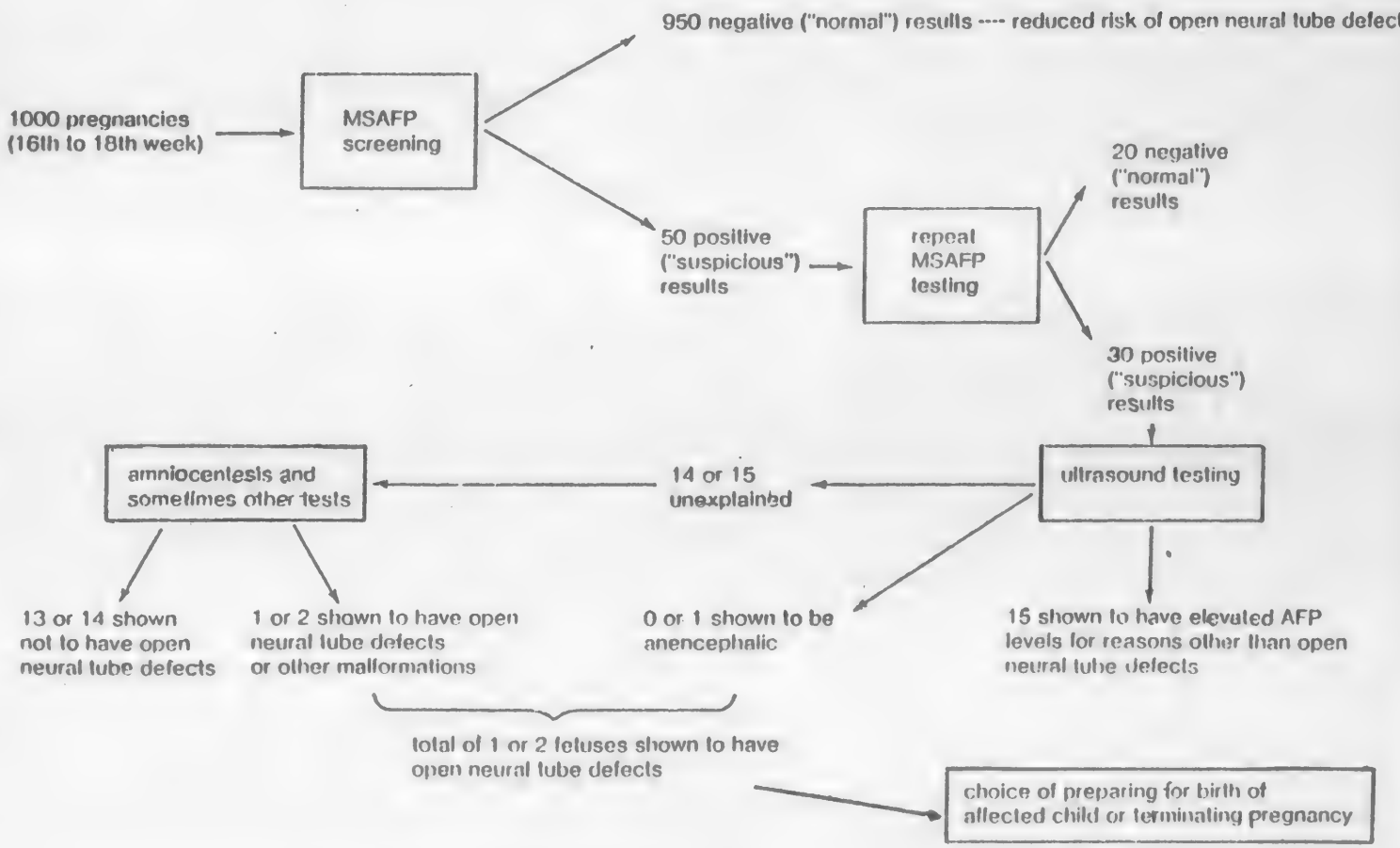
Proposed § 899.85(k) would require the laboratory to maintain a file by physician name of a copy of a signed patient acknowledgment for each sample analyzed. Proposed § 899.86(b)(4) would require the physician to submit a copy of the signed patient acknowledgment to the laboratory with each sample to be analyzed. This requirement would make the acknowledgment accessible to FDA authorized agents at a central point. This requirement would also reduce the need for FDA to visit physicians' offices to ascertain whether patient acknowledgment was obtained.

A majority of women tested will have a negative test. For these women the proposed brochure might cause some anxiety that would prove to have been unnecessary. Is this concern important enough, or are there other reasons, to choose instead a requirement that patient information be provided only if the first test is elevated (rather than before the first test)?

The proposal would require the patient to sign an acknowledgment authorizing the review and copying of her records by government officials prior to the first time blood is drawn for AFP testing. The acknowledgment would accompany any samples sent to laboratories. Is patient acknowledgment necessary for safe and effective use of AFP test kits? Would the proposed acknowledgment requirement intrude on the patient's privacy? Should "informed consent" be required instead? Or nothing? Should the patient acknowledgment accompany the sample to the laboratory or should it be sent to the program coordinator, or stay in the physician's office? Would providing such information to the government violate the patient's privacy? Would requiring the provision of such information deter women from having AFP tests performed? Could the information be limited in some way to avoid these problems?

BILLING CODE 4110-83-M

MATERNAL SERUM ALPHA-FETOPROTEIN SCREENING AND FOLLOW-UP TESTS


950 negative ("normal") results ---- reduced risk of open neural tube defects
1000 pregnancies (16th to 18th week)
MSAFP screening
50 positive ("suspicious") results
repeat MSAFP testing
20 negative ("normal") results
30 positive ("suspicious") results
ultrasound testing
14 or 15 unexplained
amniocentesis and sometimes other tests
13 or 14 shown not to have open neural tube defects
1 or 2 shown to have open neural tube defects or other malformations
0 or 1 shown to be anencephalic
15 shown to have elevated AFP levels for reasons other than open neural tube defects
total of 1 or 2 fetuses shown to have open neural tube defects
choice of preparing for birth of affected child or terminating pregnancy

The above flow chart shows the sequence of tests available in a maternal serum alpha-fetoprotein screening program. Although not indicated above, counseling also is given at each stage. The numbers on the chart are those expected if at each stage all women remaining in the high-risk category choose to undergo further testing.

BILLING CODE 4110-03-C

11. *Confidentiality of patient records.* To ensure the privacy of individually identifiable medical records, proposed § 899.83(f) would require the establishment and use of a patient identification code designed to ensure confidentiality at all levels of the program with the exception of the patient acknowledgment form. The patient identification code would be used on all patient records required by these proposed regulations. The proposal would not interfere with the use of patient names by the provider on documents, e.g., laboratory slips, on which names are customarily used. The patient code would be included on records to enable inspectors authorized by FDA to retrieve and copy documents without using the patient name.

Authorized inspectors would not ordinarily copy medical records containing the names of patients. The coordinator or his or her representative would be given the right to delete any information that could identify a patient except when: (1) FDA has reason to believe that the patient acknowledgment was not obtained; or (2) there is reason to believe that the records do not represent actual patient tests or do not represent actual results obtained. If an individually identifiable medical record is copied, the record would be properly safeguarded by FDA and would be used or disseminated under conditions that protect the privacy of the individual to the fullest possible extent, consistent with laws relating to public disclosure of information (e.g., the Freedom of Information Act and the Privacy Act) and the law enforcement responsibilities of FDA.

12. *Other elements of the AFP test Kit program.* In addition to the proposed regulation, FDA plans to publish articles of AFP testing in the "FDA Drug Bulletin" and the "FDA Consumer." ACOG plans to publish a technical bulletin on AFP testing that will be distributed to all its members.

13. *Applicability.* Proposed § 899.80 provides that the regulations apply to the use of AFP test kits to measure AFP in serum, plasma, or amniotic fluid in the prenatal detection of NTD's. Under the proposed regulations, a laboratory would be prohibited from analyzing either maternal blood serum (or plasma) or amniotic fluid using AFP test kits that are not approved by FDA or the subject of an IDE. FDA recognizes that many persons currently involved in AFP testing believe that there are methods for analyzing amniotic fluid for AFP that are preferable to the radioimmunoassay used in the test kits for which FDA approval is sought. No one has yet submitted data to FDA concerning the effectiveness of these alternative methods.

FDA has concluded that both its responsibility to protect the public and its statutory mandate dictate that it require either premarket approval applications or IDE's for these alternative tests for AFP. FDA does not wish to discourage innovation in this field and is aware of the fact that there is as yet little commercial interest in distribution of some of these tests. Thus, FDA will look favorably on properly supported requests for waiver of particular provisions of the IDE regulations with respect to the use of unapproved tests (see 21 CFR 812.10).

These proposed regulations would apply only to the use of AFP test kits to detect NTD's. They would not apply to AFP test kits labeled and sold for cancer screening or uses other than maternal serum, plasma, or amniotic fluid testing to detect NTD's. AFP test for cancer screening have been the subject of notices in the **Federal Register** of April 27, 1973 (38 FR 10488), and December 16, 1977 (42 FR 63472).

IV. Alternative Proposals

As noted above, FDA is considering other means of regulating the sale, use, and distribution of AFP test kits to provide for their safe and effective use. These include the following options:

1. *Regional pilot programs.* Some individuals, organizations, and government health agencies have urged FDA to restrict the use of AFP test kits to pilot programs serving a designated geographical area. They suggest that the high-volume testing that would occur at these regional centers is necessary for laboratory quality control and that limited pilot programs would allow for the accumulation of additional information on the test's performance prior to more extensive use of the technology.

Arguments to the contrary posit that limiting AFP testing to pilot programs would unnecessarily restrict access to the test. The proposed regulations would allow greater access to AFP testing than would occur if it were available in only a few regional centers. Second, the regional approach would require FDA to select and oversee a program for each region of the country, entailing more government involvement than seems justified. Also, concerns about high-volume laboratory testing could be addressed under the proposed regulations—if a relationship between volume and proficiency can be demonstrated—by restricting the test kits to laboratories that conduct the minimum volume of tests required by the regulations. Finally, FDA does not appear to have the authority to set up regional pilot programs per se. This could be done through funding agencies or State regulatory bodies.

Likewise, as part of the premarket approval of AFP test kits and as part of this proposal, FDA would require that data on AFP testing be submitted to the agency. The data proposed to be submitted are essentially the same as the data that would be generated by a regional pilot program. FDA believes AFP testing in foreign countries, as well as clinical trials within the United States, provides sufficient assurance about the test's safety and effectiveness to permit more extensive use of the AFP test kits while FDA monitors the test kits' performance through quarterly and annual reports.

2. *General availability.* Some persons have urged that AFP test kits be approved for unrestricted use. If this were done each manufacturer would be required (a) to develop labeling for laboratories, and prepare brochures for physicians and patients, and (b) to provide to FDA postmarketing data on each device's performance. This plan would rely on comprehensive labeling to address the issue of the availability of followup diagnostic and counseling services, the coordination of the elements of the testing, and the quality control of laboratories. No compliance program to enforce any of the labeled statements could be implemented.

3. *Physician certification to laboratories and laboratory certification to manufacturer.* A program could be adopted in which, in addition to the provisions of paragraph 2 above, any physician wishing to undertake AFP testing would have to certify to the laboratory analyzing any samples of the physician's patients, that he or she (a) has read and will follow the physician's labeling, except where medical judgment supports deviation, (b) has access to all necessary confirmatory diagnostic procedures, and (c) will make available to FDA the data described earlier in this proposal.

The laboratory would certify to the manufacturer of any AFP test kit used by the laboratory that it would accept samples only from physicians who complied with (a), (b), and (c) and that the laboratory would meet quality control criteria. This approach would be only a variant of the current proposal without use of a "program coordinator."

V. Legal Authority and Need for the Proposed Regulations

Section 520(e) of the act (21 U.S.C. 360j(e)) provides authority for the FDA (acting upon delegation of authority

from the Secretary of Health and Human Services) to restrict the use of medical devices. The issuance of the proposed regulations initiates the procedure to provide FDA authority to enforce the restrictions, if adopted, with respect to persons other than the manufacturers of AFP test kits. Thus, if the regulations that FDA is proposing in this document are made effective, any person who failed or refused to comply with the requirements, including manufacturers, laboratories, physicians, and others involved in the AFP process, would be violating the act (sections 502(q)(2); 301(a), (b), (c), (k) (21 U.S.C. 352(q)(2); 331(a), (b), (c), (k))). Publication of the proposed regulations in final form would also provide FDA other remedies under the act, besides withdrawal of the kits, if violations of the restrictions occur. Violation of restrictions imposed by regulation can result in seizure, (section 304 (21 U.S.C. 334)), injunction, (section 302 (21 U.S.C. 332)), and prosecution, (section 303 (21 U.S.C. 333)).

VI. Sunset

The proposed regulations would expire 4 years after the first approval of an AFP test kit. At the end of 4 years, the period would be extended if FDA determined that continued restrictions were necessary. Throughout the period restrictions, FDA would closely monitor the performance of the AFP test kits. Comments are especially invited on this projected "sunset" provision.

VII. Public Hearing

An open hearing will be held beginning at 9 a.m. on January 15, 1981, to give the public an opportunity to make oral comments on the proposed regulations. The hearing will be held under § 15.1(a) (21 CFR 15.1(a)), of FDA's administrative practices and procedures regulations, in the auditorium 1st floor, North Health and Human Services Building, 330 Independence Ave. SW., Washington, DC. The presiding officer will be Stuart L. Nightingale, M.D., Acting Associate Commissioner for Health Afffairs.

The purpose of the hearing is (1) to provide an open forum to present views concerning the merit of the proposed regulations and their general applicability and practicality and, (2) to foster greater consideration of the proposal among the scientific community, the regulated industry, and the public. Although the hearing will encompass all aspects of the proposal the agency seeks specific advice on the several areas of consideration discussed in the preamble above.

In preparing final regulations, FDA will consider the administrative record of this hearing along with all other written comments previously received and received during the comment period specified in this proposal.

A written notice of participation under the requirements of § 15.21 (21 CFR 15.21) must be filed with the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, not later than December 8, 1980. The notice of participation should contain Hearing Clerk Docket No. 80N–0002, the name, address, and telephone number of the person desiring to make a statement, along with any business affiliation, a summary of the scope of the presentation, and the approximate amount of time requested for the presentation (suggested to be limited to 10 minutes). To facilitate identification, the envelope containing the notice should be marked "AFP Hearing." A schedule for the hearing will be filed with the Hearing Clerk and mailed to each person who files a notice of participation within the specified filing time. Individuals and organizations with common interests are urged to consolidate or coordinate their presentations and to request time for a joint presentation.

If the response to this notice of hearing is such that insufficient time is available to accommodate the full amount of time requested in the notices of participation received, the agency will allocate the available time among the persons making the oral presentation. Formal written statements on the issues may be presented to the presiding officer on the day of the hearing for inclusion in the administrative record.

If the response to this notice of hearing is such that all persons cannot be accommodated, the hearing will be extended for an additional day, as appropriate.

The hearing will be open to the public. Any interested person may be heard on matters relevant to the issues under consideration.

FDA has established a pilot program for financial assistance to participants in certain agency proceedings, including hearings under Part 15. This program is described in regulations (21 CFR Part 10, Subpart C) that were published in the Federal Register of October 12, 1979 (44 FR 59174) and that became effective October 25, 1979 (44 FR 72585; December 14, 1979). Subject to the availability of funds and other factors, FDA may reimburse participants meeting the criteria set forth in these regulations for certain costs of participating in this proceeding. Applications for reimbursement must be filed by December 8, 1980 in accordance with § 10.210(a) (21 CFR 10.210(a)). For more information regarding the reimbursement program, contact Curtis Noah, Office of Consumer Affairs (HFE–88), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–3170.

Although reimbursement may be made available for the hearings under Part 15, the program's priority will be given to funding participating in formal evidentiary pubic hearings under Part 12 or public boards of inquiry under Part 13 of FDA's regulations (21 CFR Part 12 or 13).

As permitted by § 10.210 of FDA's public reimbursement regulations (21 CFR 10.210), the agency has established expedited procedures for review of any applications for reimbursement submitted in this proceeding. FDA will make a decision on any such applications within about 10 days after the deadline for their submission. Applicants whose applications are approved will have about 15 days to prepare for the public hearing on the AFP test kit proposal.

Conforming Amendments

FDA is proposing to amend the procedural regulations (21 CFR 16.1) regarding regulatory hearings before the FDA to add a cross-reference to the procedures proposed in this document regarding withdrawal of the enrollment for coordinator's AFP testing program.

To conform appropriately the rules on the public availability of summaries of data generated by AFP test programs, FDA purposes to add § 899.90 to the list regulations in § 20.100(c) (21 CFR 20.100(c)) that contain special rules on availability of records.

Environmental Impact

FDA has carefully considered the potential environmental impacts of this proposal and has concluded that the action will not have a significant effect on the human environment and that an environmental impact statement will not be prepared. FDA's finding of no significant impact and the evidence supporting this finding contained in an environmental assessment (pursuant to 21 CFR 25.31, proposed December 11, 1979; 44 FR 71742) may be seen in the office of the Hearing Clerk, FDA.

References

The following information has been placed in the office of the Hearing Clerk (address above) and may be seen by interested persons from 9 a.m. to 4 p.m., Monday through Friday.

(1) Erickson, J. D., "Racial Variations in the Incidence of Congenital Malformations," *Annals of Human Genetics*, 39-315, 1976.

(2) Goldberg, M. F., G. P. Oakley, "Prenatal Screening for Anencephaly-Spina Bifida: Some Epidemiologic Projection for a National Program," *in* "Service and Education in Medical Genetics," Academic Press, 1979.

(3) Brock, D. J. H., L. Barron, P. Duncan, J. B. Scrimgeour, M. Watt, "Significance of Elevated Mid-Trimester Maternal Plasma-Alpha-Fetoprotein Values," *Lancet*, June 1, 1979, pp. 1281–1282.

(4) Kjessler, B., S. G. O. Johansson, G. Lidbjork, and M. S. Sherman, "Alpha-Fetoprotein (AFP) Levels in Maternal Serum in Relation to Pregnancy Outcome in 7,158 Pregnant Women Prospectively Investigated During Their 14th-20th Week Post Last Menstrual Period," *Acta Obstet Gynecol Scand*, Suppl., 69:25–44, 1977.

(5) Hay, D. L., et al., "The Relation Between Maternal Serum Alpha-Fetoprotein and Fetomaternal Haemorrhage," British Journal of Obstetrics and *Gynaecology*, 86:516–520, 1979.

(6) McIntire, K. R., C. L. Vogel, A. Primack, T. A. Waldmann, S. K. Kyalwazi, "Effect of Surgical and Chemotherapeutic Treatment on Alpha-Fetoprotein Levels in Patients with Hepatocellular Carcinoma," *Cancer*, 37:677–683, 1976.

(7) Wald, N. J., H. Cuckle, "Maternal Serum-Alpha-Fetoprotein Measurement in Antenatal Screening for Anencephaly and Spina Bifida in Early Pregnancy," *Lancet*, June 25, 1977, pp. 1323-1332.

(8) Wald, N. J., H. S. Cuckle, "Amniotic-Fluid Alpha-Fetoprotein Measurement in Antenatal Diagnosis of Anencephaly and Open Spina Bifida in Early Pregnancy," *Lancet*, September 29, 1979, pp. 651–661.

(9) Letter dated 8 Aout (August), 1979, from Mme. Hermine Nagel to Monsieur Michel Bernon.

(10) Letter dated July 27, 1979, from Markku Seppala, M.D., to Dr. Alison Carlson.

(10a) Report by the Working Group on Screening for Neural Tube Defects, July, 1979 Department of Health and Social Security, Health Notice No. HN(79)116, London, England.

(11) Milunsky et al., "Prenatal Diagnosis of Neural Tube Defects IV. Maternal Serum Alpha-Fetoprotein Screening," *Obstetrics and Gynecology*, 55-60–66, January 1980.

(12) Cowchok, F. S. and L. G. Jackson, "An Analysis of Pregnancies With Elevated Alpha-Fetoprotein Levels in Maternal Serum and/or Amniotic Fluid Samples," *Birth Defects*, 15:75–85, 1979.

(12a) Smith, A. D., et al., "Amniotic-Fluid Acetylcholinesterase as a Possible Diagnostic Test for Neural-Tube Defects in Early Pregnancy," *Lancet*, March 31, 1979, pp. 685–687.

(13) Letter dated April 16, 1979, from Ervin E. Nichols, M.D., to Donald Kennedy, Ph.D.

(14) Letter dated April 13, 1979, from Charles Scriver, M.D., to Donald Kennedy, Commissioner, Food and Drug Administration.

(15) Letter dated May 2, 1979, from Jean H. Priest, M.D., to Donald Kennedy, Commissioner, FDA.

(16) Statement by Mrs. Carol Buchholz and Mr. Thomas Tapke on behalf of the Spina Bifida Association of America at the February 26, 1979, public hearing on AFP.

(17) April 23, 1979 letter and enclosed petition from Robert B. Leflar, Staff Attorney, and Sidney M. Wolfe, M.D., Public Citizen Health Research Group, to Dr. Donald Kennedy, Commissioner, Food and Drug Administration.

(18) Memorandum dated March 9, 1979, from Director, Center for Disease Control, to Ms. Ruth Hanft.

(19) Statement by Health Services Administration on Issues Relating to AFP Tests for FDA Public Meeting on February 26, 1979.

(20) "Antenatal Diagnosis," report of a Consensus Development Conference, National Institutes of Health, NIH Publication No. 79–1973, April 1979.

(21) Letter dated February 1, 1980 from Dr. John L. Hamerton, D.Sc., F.C.C.M.G., to Dr. Renie Schapiro.

(22) Report of the ACOG/AAP Alpha-Fetoprotein Task Force, August 3, 1979.

(23) Letter dated July 26, 1979 from Carol Buchholz, to Mark Novitch, M.D.

(24) Macri, J. N., J. E. Haddow, and R. R. Weiss, "Screening for Neural Tube Defects in the United States. A Summary of the Scarborough Conference," *American Journal of Obstetrics and Gynecology*, 133:119, 1979.

(25) Alpha-Fetoprotein (AFP) Testing Program Facilities Survey, sponsored by Wampole Laboratories, Division of Carter-Wallace, Inc.

(26) Roney, P. L. and R. M. Albrecht, "Hospital Survey of Obstetric Ultrasound-United States, 1974," *in* "Symposium on Biological Effects and Characterizations of Ultrasound Sources," HEW Publication (FDA) 78–8048, December 1977.

(27) "Ultrasound Forum '79," conducted by Technology Marketing Group Ltd., reported in Radiology/Nuclear Medicine Magazine, August 1979, pp. 4–24.

(28) "User Training for Obstetric and Gynecologic Ultrasound Diagnosis by Physicians," Society of Obstetric and Gynecologic Ultrasound response to Notice of Intent of FDA, (Docket No. 78N–0288), Federal Register, 44 FR 9542; February 13, 1979.

(29) Letter dated August 28, 1979, from Robert B. Leflar, Staff Attorney, and Sidney M. Wolfe, M.D., to Mark Novitch, M.D.

(30) "Editorial," *Journal of Clinical Ultrasound*, 6(2):73–75, 1978.

(31) McKinney, William M., "Editorial," *Journal of Clinical Ultrasound*, 4(1):1–2, 1976.

(32) Wilson, Robert L., "Editorial," *Reflections*, 4(2):66, 1978.

(33) Lyons, E. A., "Guest Editorial," *Reflections*, 5(2):11, 1979.

(34) Memorandum dated June 12, 1979, to Director, Bureau of Medical Devices from Administrator, Health Services Administration.

(35) Letter dated November 14, 1979, from Duane Alexander, M.D., to Renie Schapiro.

(36) Letter dated May 14, 1979, from Ervin Nichols, M.D., American College of Obstetricians and Gynecologists to Donald Kennedy, Ph.D., Commissioner, Food and Drug Administration.

(37) Wald, N. J., H. S. Cuckle, and B. Stoll, "Antenatal Screening and Diagnosis of Open Neural-Tube Defects—Quality Control of Alpha-Fetoprotein Reagents and Assay," (in press) *Clinica Chemica Acta*, 1980.

(38) Memorandum dated January 7, 1980. from Stephen W. Smith, Ph.D., to Staff Fellow, Office of Health Affairs, FDA.

(39) Letter dated October 22, 1979, from Marc S. Lapayowker, M.D., American College of Radiology, to Mark Novitch, M.D.

(40) "System Design of a Clinical Facility for Diagnostic Ultrasound," prepared by Alliance for Engineering in Medicine and Biology, September 1977.

(41) Letter dated June 13, 1980, from Joseph D. Schulman, M.D., National Institutes of Health, to Mark Novitch, M.D.

(42) Memorandum dated August 4, 1980 from Joseph D. Schulman, M.D. to Mark Novitch, M.D. and Seymour Perry, M.D.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 520(e), 701(a), 52 Stat. 1055, 90 Stat. 567 (21 U.S.C. 360j(e), 371(a))) and under authority delegated to the Commissioner (21 CFR 5.1), it is proposed that Chapter I of Title 21 of the Code of Federal Regulations be amended as follows:

PART 16—REGULATORY HEARING BEFORE THE FOOD AND DRUG ADMINISTRATION

1. In Part 16, § 16.1(b)(2) is amended by adding the following:

§ 16.1 Scope.

* * * * *

(b) * * *

(2) * * * § 899.82(d), relating to withdrawal of the enrollment for a coordinator's alpha-fedoprotein testing program.

* * * * *

PART 20—PUBLIC INFORMATION

2. In Part 20, by adding new paragraph (c)(34) to § 20.100, to read as follows:

§ 20.100 Applicability; cross-reference to other regulations.

* * * * *

(c) * * *

(34) Data and information submitted in periodic reports for alpha-fetoprotein test kits, in § 899.90 of this chapter.

* * * * *

3. By adding new Part 899, to read as follows:

PART 899—RESTRICTED DEVICES

Subparts A–D [Reserved]

Subpart E—Alpha-Fetoprotein Test Kits

Sec.

899.80 Definitions.
899.81 Designation as restricted device; specific restrictions.
899.82 Enrollment of AFP testing programs.
899.83 Responsibility of program coordinators.
899.84 Restrictions on manufacturers.
899.85 Restrictions on laboratories.

899.86 Restrictions on physicians.
899.87 Restrictions on ultrasonography and amniocentesis facilities.
899.88 Permission to inspect.
899.89 Record retention.
899.90 Release of information.

Subparts A–D [Reserved]

Subpart E—Alpha-Fetoprotein Test Kits

§ 899.80 Definitions.

As used in this subpart:

"AFP test kit" means reagents and other materials for use in the diagnosis of neural tube defects in fetuses by analysis of the amount of alpha-fetoprotein (AFP) in the blood serum (or plasma) and amniotic fluid of pregnant women;

"AFP testing program" means all services that are covered by the certification made by a coordinator pursuant to § 899.82;

"Coordinator" means an individual who, on behalf of a program, makes the written certification required by § 899.82

§ 899.81 Designation as restricted device; specific restrictions.

(a) AFP test kits are restricted devices.

(b) AFP test kits may be distributed, sold, or used only in compliance with an approved investigational device exemption application under Part 812, or in compliance with the specific restrictions set out in this subpart.

§ 899.82 Enrollment of AFP testing programs.

(a) To initiate an AFP testing program, a coordinator shall certify in writing to the Bureau of Medical Devices, Division of Clinical Laboratory Devices (HFK–440), Food and Drug Administration, 8757 Georgia Ave., Silver Spring, MD 20910, that he or she is capable of complying and will comply with the requirements of this section and §§ 899.83, 899.88, and 899.89. The certification shall contain the coordinator's name, address, and telephone number and shall state that the facilities referred to in § 899.83(a) either (1) exist within an organization, such as a hospital or medical center, of which the coordinator is an authorized representative, or (2) have agreed in writing to provide services to patients within the AFP testing program and to comply with applicable provisions of this subpart.

(b) When a certification under paragraph (a) of this section has been submitted, the Food and Drug Administration (FDA) will review it and if not deficient, will enroll the AFP testing program, and will provide an enrollment number to the coordinator. Upon receiving an enrollment number, the coordinator shall inform each physician and laboratory associated with his or her program of that enrollment number.

(c) If the coordinator determines that the certification made pursuant to paragraph (a) of this section can no longer truthfully be made, the coordinator shall notify FDA and all persons associated with the program that the enrollment of that program is terminated.

(d) Whenever FDA has reason to believe that the certification made by a coordinator under paragraph (a) of this section was not made truthfully or, because of changed circumstances, can no longer be truthfully made—

(1) The Director of the Bureau of Medical Devices (the Director) will furnish the coordinator written notice of the matter complained of in general terms and offer the coordinator an opportunity to explain the matter informally or in writing;

(2) If an explanation is offered but not accepted by the Director, the coordinator shall have an opportunity for a regulatory hearing before FDA, pursuant to Part 16 of this chapter, on the question of whether the enrollment for the coordinator's AFP testing program should be withdrawn;

(3) If, after evaluating all available information, the Commissioner of Food and Drugs determines that the certification made by the coordinator was not true when made or can no longer truthfully be made, the Commissioner will withdraw the enrollment of that coordinator's AFP testing program;

(4) If, in the judgment of the Director, the alleged deviations from the certification required to be made by the coordinator are such that they place patients involved in the coordinator's AFP testing program at significant risk, the Director may withdraw the enrollment of the coordinator's AFP testing program prior to, and pending completion of, a regulatory hearing; in such case, the regulatory hearing will be expedited.

(5) The remedies provided by § 899.82(d) shall be in addition to other remedies provided for enforcement of the restrictions contained in this subpart.

§ 899.83 Responsibility of program coordinators.

(a) Each coordinator of an AFP testing program shall assure that there is available to each patient utilizing the program, as needed, all of the following—

(1) A laboratory that has agreed to comply with the requirements of §§ 899.85, 899.88, and 899.89;

(2) Ultrasonography capable of identifying multiple fetuses and anencephaly, detecting fetal death, and determining gestational age at a facility that has agreed to comply with the requirements of §§ 899.87, 899.88, and 899.89;

(3) Amniocentesis for the purpose of obtaining amniotic fluid to measure AFP at a facility that has agreed to comply with requirements of §§ 899.87, 899.88, and 899.89;

(4) Appropriate counseling for all women who are considering participation or who participate in the AFP testing program, including a description of the risks associated with the testing procedures, the significance of the test results, the range of severity of neural tube defects, and the options available to the patient.

(b) Each coordinator shall establish a procedure for providing all physicians participating in that coordinator's AFP testing program with professional and patient brochures prepared by the manufacturer and approved by FDA.

(c) Each coordinator shall make arrangements to receive timely notification of any test result on a patient within the coordinator's program which suggests either that the patient carries a fetus with a neural tube defect or that further testing is appropriate, e.g., an elevated result from analysis of a maternal serum specimen or an ultrasonography test that fails to account for high AFP serum levels as resulting from causes other than a neural tube defect.

(d) Each coordinator shall secure agreements from each physician associated with that coordinator's program that the physician will:

(1) Notify the coordinator of the pregnancy outcome for any patient with an AFP test result greater than 2.5x the median,

(2) Notify the coordinator if any patient involved in the AFP testing program has a pregnancy involving a fetus with a neural tube defect or any other condition associated with elevated AFP,

(3) Notify the coordinator if any patient has an induced or spontaneous abortion within 3 weeks of an amniocentesis performed to obtain amniotic fluid upon which to measure AFP, and

(4) Make available to the coordinator, as requested, all data related to AFP testing of that physician's patients within that coordinator's program, including copies of patient

acknowledgments, as required by § 899.86(d).

(e) Each coordinator shall furnish to each manufacturer of an AFP test kit used by a laboratory within that coordinator's program, 15 days before the manufacturer is required to submit the quarterly report, current data required by FDA as part of the approval of premarket approval applications for such AFP test kit(s). In addition, the coordinator shall furnish to each manufacturer, for inclusion in its report, the information required by § 899.83(g) within 35 days of amniocentesis for each patient who undergoes amniocentesis to obtain amniotic fluid for measuring AFP.

(f) Each coordinator shall establish and implement written procedures for coding the identification of patients within the program to ensure the confidentiality of patient records.

(g) Each coordinator shall maintain, for each woman who has a result greater than 2.5x the median in any AFP test or who is tested for AFP and whose pregnancy involves a fetus that has a neural tube defect or any other condition associated with elevated AFP, records listing, as applicable:

(1) Patient code;

(2) Physician identification;

(3) Date of initial test and estimated gestational age on that data;

(4) For each serum and amniotic fluid test—

(i) Result in mass units or in International Units and in multiples of the normal median value at the same gestational week;

(ii) Designation of that result as greater or less than 2.5x the median;

(iii) Identification of the facility that performed each test;

(iv) For an amniotic fluid test, identification of the facility at which amniotic fluid was withdrawn;

(v) Relation of fetus to any first or second degree family relative with anencephaly or spina bifida;

(5) For each amniotic fluid test—

(i) Age, race, and county and State of residence of patient;

(ii) Specific indication for test, or other test performed, where primary indication for amniocentesis was not to measure AFP;

(6) For each ultrasonography examination—

(i) Whether the pregnancy involved a single fetus or multiple fetuses;

(ii) Whether the pregnancy involved fetal death;

(iii) Gestational age as determined by ultrasonography;

(iv) Identification of the facility that performed the examination;

(v) Whether the fetus or fetuses have anencephaly or other defects;

(7) Statement of whether or not the pregnancy involved a fetus with a neural tube defect or any other condition associated with elevated AFP.

(h) Each coordinator shall make arrangements to receive timely (within 1 week of the abortion) reports of any pathologic examination of the fetus for the presence of external congenital malformations following any spontaneous induced abortion occurring within 3 weeks after an amniocentesis performed to obtain amniotic fluid upon which to measure AFP.

§ 899.84 Restrictions on manufacturers.

Each manufacturer of an AFP test kit shall—

(a) Distribute any AFP test kit—other than for investigational use in compliance with Part 812—only to laboratories that are associated with an enrolled AFP testing program and that notify the manufacturer of the enrollment number of that program;

(b) Prepare and provide to coordinators at their request professional brochures and patient brochures approved by FDA;

(c) Submit quarterly and annual reports to the Bureau of Medical Devices, Division of Clinical Laboratory Devices (HFK–440), Food and Drug Administration, 8757 Georgia Ave., Silver Spring, MD 20910, of data generated by those programs using that manufacturer's AFP test kit as specified in the approval of that manufacturer's premarket approval application for its AFP test kit;

(d) Maintain distribution records for each AFP test kit distributed by that manufacturer under the provisions of § 899.84(a) that include, or identify the location of, the name and address of the consignee, the consignee's enrollment number, the date shipped, and the control number used.

§ 899.85 Restrictions on laboratories.[1]

Each laboratory using an AFP test kit shall—

(a) Measure AFP for the purpose of testing for neural tube defects only by use of—

(1) An AFP test kit approved by FDA pursuant to 21 U.S.C. 360e, or

(2) An AFP test kit for which an investigational device exemption application has been approved pursuant to Part 812;

(b) Use AFP test kits to analyze only samples submitted by physicians who are part of an AFP testing program with which the laboratory is associated and who demonstrate that fact by including the enrollment number for the program with each sample submitted;

(c) Follow the product labeling prepared by the manufacturer of the AFP test kit used and approved by FDA except where there is a clear justification for using alternative procedures;

(d) Participate satisfactorily in—

(1) A laboratory inspection program authorized by FDA, and

(2) A proficiency testing program established by the Center for Disease Control or the College of American Pathologists or one endorsed by FDA.

(e) Within 1 year after enrollment in the program, test a minimum total of 50 of any combination of maternal serum and amniotic fluid samples each week.

(f) For each AFP test performed, maintain, or identify the location within the program of, separate records that include—

(1) Type of specimen (i.e., serum or amniotic fluid);

(2) Sample identification;

(3) Physician identification;

(4) Program number;

(5) Patient code;

(6) Date test performed;

(7) Estimated week of gestation on date specimen drawn;

(8) Result (numerical and as a multiple of the median value);

(9) Identity of AFP test kit manufacturer and control number of the AFP test kit used in the test;

(10) Median value used;

(11) Quantitation of fetal blood, if any, in amniotic fluid samples.

(g) Until it has established its own normal median values, maintain, or identify the location within the program of, separate records of samples having values greater than 2.5x the median that were referred to another laboratory, which records shall include—

(1) Original sample identification;

(2) Program number of laboratory to which sample is referred;

(3) Date test performed by laboratory to which sample is referred;

(4) Result obtained by laboratory to which sample is referred (numerical and as a multiple of the median value);

(5) Identity of AFP kit manufacturer and control number of the AFP test kit used by laboratory to which the sample is referred;

(6) Median value used;

(7) Quantitation of fetal blood, if any, in amniotic fluid samples.

(h) Document the establishment of normal median values for each manufacturer's AFP test kit that the laboratory uses;

(i) Notify immediately by telephone (and confirm in writing) both the coordinator and the attending physician

[1] See also 42 CFR 74.22 and 42 CFR 405.1317.

of any test result greater than 2.5x the median;

(j) Make available to each coordinator, as requested, all data related to AFP testing by that laboratory of patients within that coordinator's program; and

(k) Maintain a file by physician name containing a copy of the signed patient acknowledgement for each sample analyzed.

§ 899.86 Restrictions on physicians.

Each physician participating in an enrolled AFP testing program shall—

(a) Obtain from each patient, prior to taking the sample for the first AFP test, acknowledgment, by signature and date on a document that contains the patient's code, that the patient has—

(1) Been provided an approved patient brochure;

(2) Been provided an opportunity to discuss AFP testing and neural tube defects generally with the physician or with a counselor familiar with the subject;

(3) Authorized review and copying of her records by authorized agents of FDA, if necessary, for compliance purposes.

(b) Include with each sample submitted to a laboratory for analysis—

(1) Enrollment number of the program with which the physician is associated;

(2) Patient code;

(3) Estimated week of gestation on date specimen drawn;

(4) A copy of the signed patient acknowledgement;

(c) Notify the coordinator immediately of—

(1) Any pregnancy involving a fetus with a neural tube defect or other condition associated with elevated AFP;

(2) The pregnancy outcome of all women who have a result greater than 2.5x the median in an AFP test;

(d) Make available to the coordinator, as requested, all data related to AFP testing of that physician's patients within that coordinator's program, including copies of patient acknowledgments;

(e) Maintain records for each of that physician's patients involved in AFP testing which include—

(1) Signed patient acknowledgment documents;

(2) For all AFP-related tests, including any followup amniocentesis, ultrasound or other confirmatory tests—

(i) Type of test;

(ii) Date specimen drawn for serum and fluid tests and date of testing for all other tests;

(iii) Identification of testing facility;

(iv) Test result;

(v) Patient code;

(3) Record of whether or not the pregnancy involved a fetus with a neural tube defect or any other condition associated with elevated AFP;

(4) Program enrollment number;

(5) Estimated gestational age for serum and fluid tests and record of how that age was determined for each such test.

§ 899.87 Restrictions on ultrasonography and amniocentesis facilities.

Each ultrasonography and amniocentesis facility that performs confirmatory tests on any patient as a result of that patient's participation in AFP testing shall—

(a) For each AFP-related test performed, maintain, or identify the location within the program of, records that include:

(1) Type of test and date performed;

(2) Patient code;

(3) Identification of patient's physician;

(4) Program enrollment number;

(5) For each ultrasonography examination—

(i) Whether the pregnancy involves a single fetus or multiple fetuses;

(ii) Whether the pregnancy involves fetal death;

(iii) Gestational age as determined by ultrasonography;

(iv) Whether the pregnancy involves anencephaly or other defects;

(6) Identification of the individual who performed the test;

(b) Make available to each coordinator, as requested, all data related to AFP testing by that facility of patients within that coordinator's program.

§ 899.88 Permission to inspect.

Any coordinator, laboratory, physician, amniocentesis facility, or ultrasonography facility associated with an AFP testing program shall permit authorized agents of FDA—

(a) To inspect the person's establishment at reasonable times and in a reasonable manner; and

(b) To have access to and to copy all records relating to AFP testing.

§ 899.89 Record retention.

All records required to be maintained as part of an AFP testing program shall be retained until 2 years following the expiration of the regulations in this subpart.

§ 899.90 Release of information.

FDA will release to the public summaries of data from AFP test programs submitted by manufacturers. These summaries will, if feasible, report results by AFP test program and by manufacturer.

Interested persons may, on or before January 6, 1981, submit to the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments regarding this proposal. Four copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the Hearing Clerk docket number found in brackets in the heading of this document. Received comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

The restrictions that are being proposed by informal rulemaking under section 520(e) of the act (21 U.S.C. 360j(e)) are essentially the same as those that are part of the premarket approval of the device under section 515 of the act (21 U.S.C. 360e). The reason for the additional rulemaking is to expand the reach of the restrictions to ensure the safe and effective use of the device. FDA will only approve the device if its safe and effective use can be ensured by the restrictions being imposed under section 520(e) of the act. Thus, those restrictions are functionally, if not technically, part of the approval process. Under the act, the premarket approval of a drug for human use, a veterinary drug, or a class III device, is a licensing decision ("adjudication"), not a regulation ("rule"). Because Executive Order 12044 only applies to regulations, it does not require regulatory analyses for premarket approval decisions for these products. FDA has concluded that a regulatory analysis is not required for a regulation that imposes the same restrictions as those that were conditions to premarket approval, and whose purpose is to expand the reach of these conditions.

Furthermore, because the preamble to the proposed regulation identifies and discusses thoroughly several alternatives to the proposed restrictions and their impacts, FDA has determined that preparation of a discretionary regulatory analysis would contribute nothing further at this stage of the development of the regulation. It should be noted, however, that in addition to reviewing written comments on the proposal, FDA will hold a public hearing to afford interested persons the opportunity to discuss the proposed restrictions, their impact, and alternatives.

Dated: September 26, 1980.

Mark Novitch,

Acting Commissioner of Food and Drugs.

[FR Doc. 80–34052 Filed 11–6–80; 8:45 am]

BILLING CODE 4110–03–M

Public Health Service

Health Care Financing Administration

42 CFR Parts 74 and 405

Clinical Laboratories: Quality Control Standards Regarding Alpha-Fetoprotein Test Kits

AGENCIES: Center for Disease Control, Public Health Service, and Health Care Financing Administration, Department of Health and Human Services.

ACTION: Notice of Proposed Rulemaking.

SUMMARY: See the notice of Proposed Rulemaking by the Food and Drug Administration (FDA), immediately preceding this Notice, in which the FDA proposes conditions for marketing commercial test kits for use by clinical laboratories in measuring alpha-fetoprotein (AFP) levels in maternal sera, plasma, and amniotic fluid. In this Notice, the Department proposes additional quality control and testing requirements applicable to AFP testing for the prenatal detection of fetal neural tube defects conducted by laboratories licensed under the Clinical Laboratories Improvement Act of 1967 (CLIA) and laboratories certified for reimbursement under Title XVIII of the Social Security Act (Medicare).

DATE: Comments must be received on or before January 6, 1981.

ADDRESS: Comments or inquiries may be submitted to: Dr. Joseph H. Boutwell, Deputy Director, Bureau of Laboratories, Center for Disease Control, 1600 Clifton Road, NE., Atlanta, Georgia 30333. Comments will be available for public inspection at this address between 8 a.m. and 4:30 p.m. Monday through Friday (except holidays).

FOR FURTHER INFORMATION CONTACT: Dr. Joseph H. Boutwell (404) 329–3263 or FTS 236–3263.

SUPPLEMENTARY INFORMATION:

Background

The purpose of this Notice is to propose addtional quality control and testing requirements with respect to AFP testing. As discussed in the FDA NPRM immediately preceding this Notice, it has been determined that the additional quality control and testing requirements proposed in the NPRM are necessary in order to assure the safe and effective use of AFP testing kits.

Provision of the Regulations

Current quality control regulations include requirements of a general nature which are applicable to AFP testing. Because of the tentative FDA decision, which has the potential for increasing the application of AFP testing technology, it is necessary to amend the current regulations to include additional quality control testing requirements of a more specific nature in order that this technology may be safely and effectively used in clinical laboratories which have little or no experience in this test procedure. The proposed provisions are regarded as good laboratory practice and employed by many laboratories presently doing this test.

New requirements of a substantive nature indlude:

- The provision of specified demographic and epidemiolgic data in order to assure that the physician can be provided with the information required for valid interpretation values by specific gestational week for maternal sera, plasma, and amniotic fluid and to provide the basis for method validation;
- Confirmation of positive results by a referral laboratory while normal median values are being developed in order to assure proper interpretation of patient results while relevant local norms are being developed;
- Specification of minimum weekly workload requirements for testing maternal sera, plasma, and amniotic fluid to insure the timely development and continued current maintenance of local normative data for patient interpretation;
- A specification that serum specimens are not to be tested for neural tube defect screening except during the 15th through 22nd completed gestational weeks;
- The use of a specified number of calibrators and controls sufficient to insure accurate and reproducible patient results;
- Patient specimens to be tested in duplicate to increase the assurance against the possibility of aberrant results not detected by the usual quality control system.

Some of these new AFP requirements (including the mandatory submission of patient data and the minimum weekly workload requirements) are more stringent quality control measures than those which are currently applied to other laboratory procedures. These stricter quality control measures are necessary because of the potentially serious consequences that could arise out of inaccurate AFP testing. Such undesirable consequences, as pointed out in the accompanying FDA NPRM, include therapeutic abortion of normal fetuses, failure to identify affected fetuses, and women becoming unnecessarily alarmed about the outcome of their pregnancies.

Applicability

CDC/HCFA regulations apply to the performance of AFP tests without regard to the nature of the procedure used or the source of reagents used. Certain details with respect to reporting the results of AFP testing (for fetal abnormalities) in 42 CFR 74.22(d)(1)(xii) and 74.22(d)(4)(i), and possibly other sections, may be modified if alternative proposals (FDA NPRM Preamble, IV) are adopted.

Expanded Patient Data and Minimum Workload Requirements

The Department has decided that it is necessary for the laboratory to require that some additional patient data accompany the patient specimen. This is essential to insure correct patient identification and to insure that the physician is provided correct and appropriate results related to the normal expected results which may vary by gestational age of the fetus, race, family history, geographic variations, and source of specimen (maternal sera, plasma, or amniotic fluid). Unless complete relevant information accompanies the test result, the patient may be inappropriately subjected to the further risks of sonography and amniocentesis and to the emotional trauma of considering the relative merits of terminating the pregnancy. We invite comments on whether these data requirements are necessary for the safe and effective use of AFP tests. We also invite comments as to whether requiring this information intrudes on a patient's privacy and deters her use of an AFP test or, on the other hand, whether any additional information should be required in order to assure a more accurate interpretation of the laboratory results.

The Department has determined that the required accuracy of results cannot be assured unless laboratories performing AFP testing do so with a reasonable frequency and in sufficient numbers to provide accuracy of performance and the data for the required internal cross correlations. The FDA notice which appears elsewhere in this issue of the **Federal Register** summarizes the various points of view on appropriate workload requirements. The Department invites comments on whether these requirements are necessary to assure the quality of laboratory performance. The Department also invites comments on the specific minimum workload requirements proposed in this notice and the effect of those requirements on the ability of laboratories to participate in AFP testing.

Use of Non-Commercial Reagents for AFP Testing

The question has arisen as to whether laboratories should be permitted to use reagents other than those included in a commercial test kit. Clinical laboratory quality control regulations are intended to insure the quality of performance of laboratory tests regardless of the source of the reagents employed in such tests. Accordingly, it is the Department's intent that these quality control requirements should apply to AFP testing using either commercial or noncommercial reagents. It should be noted that these proposed regulations require that the method used to measure AFP levels must rely on a working curve which has been calibrated against the World Health Organization Standard for AFP (72–225), or its equivalent. The calibration process must also be documented.

Interagency Agreement Between the Public Health Service (PHS) and the Health Care Financing Administration (HCFA)

Under an Interagency Agreement between the PHS and HCFA, approved on March 17, 1979, for administration of Departmental regulatory programs affecting clinical laboratories, the Center for Disease Control is responsible for developing scientific and technical standards in the areas of quality control, proficiency testing, personnel requirements, and records, equipment and facilities; conducting a program of proficiency testing for laboratories licensed under the Clinical Laboratories Improvement Act of 1967; monitoring the performance of State Agencies and approved accreditation bodies to evaluate effectiveness and uniformity in the application of standards; and determination of training needs and design and presentation of seminars and courses for State Agency surveyors, HCFA regional office laboratory specialists, and representatives of approved accreditation bodies.

HCFA responsibilities under the Interagency Agreement include the initial surveys and annual resurveys of CLIA licensed and Medicare certified laboratories, working through State Agencies and other accrediting bodies; the issuance of licenses and necessary certification documents; and the execution of any adverse actions which may be necessary with respect to the termination or limitation of licenses, or the Medicare certification status, of clinical laboratories.

AFP Proficiency Testing

The Center for Disease Control (CDC) is developing a proficiency testing program for AFP which can be operational within 90 days of publication of this NPRM. For a period of time, this proficiency testing program will be operated on an experimental basis in order to develop data with respect to an appropriate grading system and to develop appropriately referenced samples with sufficient stability so that they can be distributed through the mail systems.

The CDC program will assign a gestational week to each of the proficiency testing samples and then ask for a laboratory assessment of "normal" or "abnormal" which will be compared with an evaluation of the same materials by a panel of experts.

Until such time as other proficiency testing programs, such as the one conducted by the College of American Pathologists, are operational, CDC will provide proficiency testing services to Medicare certified laboratories upon request by HCFA.

Cost Implications

We estimate the cost of the proposed quality control and testing requirements for AFP testing in a laboratory performing at a minimal workload (50 per week) to be no more than 10–15 percent of the cost of performing the tests, or about $300–$500 per year. One manufacturer has estimated that the proposed restrictions would increase the cost of a test kit by 50 percent, for example, from $150 to $225 for a kit that can be used for 40 patients. We invite comments on the accuracy of our estimates of the costs of complying with the proposed quality control requirements and on whether those additional costs are justified.

It is anticipated that some laboratories, particularly some smaller facilities, that might otherwise be interested in performing AFP testing, may choose not to engage in such testing because they might find it difficult to meet, and to comply with on a continuing basis, the quality control and testing requirements that are set forth in the attached NPRM. Accordingly, it is possible that the supply of laboratories qualified to perform AFP testing services may not be sufficient to meet the demand for these services, and further, that the market forces in such a situation could result in the escalation of the cost of AFP testing services.

The Department invites comment on the cost implications of the proposed requirements, their impact on small laboratories, and their effect on the supply of AFP testing services.

Recordkeeping and Reporting Requirements

The recordkeeping and reporting requirements to be included in the final rule will be submitted for approval by the Office of Management and Budget (OMB) in accordance with the Federal Reports Act of 1942 (44 U.S.C. 3501 et seq.). OMB approval will be obtained before the recordkeeping and reporting requirements are implemented.

It is, therefore, proposed to amend Parts 74 and 405 of Title 42, Code of Federal Regulations, as set forth below.

Dated: May 27, 1980.

Julius B. Richmond,

Assistant Secretary for Health.

Dated: June 4, 1980.

Earl M. Collier, Jr.,

Acting Administrator, Health Care Financing Administration.

Approved: October 21, 1980.

Patricia Roberts Harris,

Secretary.

PART 74—CLINICAL LABORATORIES

It is proposed to amend 42 CFR Part 74 as follows:

Section 74.22 is amended by adding a new paragraph (d) which reads as follows:

§ 74.22 Serology.

* * * * *

(d) The following requirements are applicable to screening and diagnostic tests to determine alpha-fetoprotein (AFP) levels on sera, plasma, or amniotic fluid obtained from pregnant patients.

(1) The laboratory's requisition form for AFP testing must provide for the following information:

(i) Name of the person from whom the specimen was taken.

(ii) State and county of residence of person from whom the specimen was taken.

(iii) Age of person from whom the specimen was taken.

(iv) Race/ethnicity of person from whom the specimen was taken.

(v) Date the specimen was collected and the nearest gestational age of the fetus calculated in weeks from the first day of the last menstrual period.

(vi) Source of specimen (maternal sera, plasma, or amniotic fluid).

(vii) Indication of whether the specimen is the first specimen or a repeat specimen.

(viii) Relation of fetus to any first or second degree family member relative with anencephaly or spina bifida.

(ix) Identification of any preservative added to the specimen, concentration, and the consequent dilution of the specimen if greater than one percent.

(x) For amniotic fluid, a statement indicating that the specimen has not been centrifuged; or, if it has, an evaluation of the whole fluid (uncentrifuged) has been made for the presence of fetal red blood cells of fetal hemoglobin by the shipper. The results of that evaluation must accompany the specimen.

(xi) Name and address of person, clinic, center, or laboratory submitting the specimen.

(xii) A statement specifying that a report will not be issued unless the name of the patient and items (v), (vi), (vii), (ix), (x), and (xi) are provided to the laboratory. Items (ii), (iii), (iv), and (viii) do not have to be provided to the laboratory if the physician, coordinator, or laboratory determines that the lack of such information does not jeopardize the identification of that patient or the interpretation of the test results for the patient.

(2) The following requirements apply to AFP testing of maternal serum or plasma specimens:

(i) Only those serum or plasma specimens taken between the 15th and 22nd gestational week as measured from the first day of the last menstrual period may be used for testing. The report (phoned and written) shall include the patient's name, type of specimen, numerical value of the test result as a multiple of the normal median value at the same gestational week, and the equivalent mass or international units.

(ii) The laboratory must validate its own serum AFP method by assaying at least 100 normal maternal serum or plasma specimens at each gestational week between the 15th and 22nd weeks measured from the first day of the last menstrual period and document the median AFP levels for each gestational week. While normal values are being determined, a laboratory may use the normal values specified in the manufacturer's package insert. An elevated value must be confirmed, however, with repeat testing by a laboratory which has established its own normal values. If commercial kits are used, the medians determined by the laboratory must fall within 10 percent of those stated in the manufacturer's literature. The laboratory must maintain its competency by assaying a total of at least 50 mid-pregnancy patient specimens, in duplicate, per week. Maternal serum, plasma, and amniotic fluid specimens may all be counted for purposes of attaining this stated minimum workload level. The laboratory must attain the stated minimum workload level within 12 months of licensure or certification to provide AFP services.

(iii) The laboratory must document that the alpha-fetoprotein working curve has been calibrated against the World Health Organization Standard for AFP (72–225) or its equivalent within the lifetime of the working curve. The laboratory must perform its own calibration against the World Health Organization Standard or equivalent for its working curve or use a working curve certified by the manufacturer to have been calibrated against the World Health Organization Standard. At least a six point dose response regression analysis (3 dilutions in duplicate per curve) must be used in this calibration comparison to permit a valid statistical evaluation of the results. Each analytical run must contain at least 5 dilutions of the laboratory's AFP calibrator covering a range of at least 0.5 times to 8.0 times the median AFP level of the unaffected pregnancies at the 17th week of gestation. At least three quality control sera must be assayed in duplicate in each analytical run. The respective concentrations of AFP used for control purposes must have values near the median mid-pregnancy maternal serum AFP concentration of normal unaffected population at the 17th weeks, near the maternal serum positive screening cut off value at 2.5 times the unaffected population median at the same gestational age, and near the median pathological level for spina bifida at 4 times the unaffected population median. Patient specimens must be tested in duplicate. Control limits for calibrators and reference samples shall be recorded and displayed and shall include the course of action to be instituted when the results are outside of acceptable limits. The limits may not be less stringent than those recommended by the manufacturer in the package insert.

(3) The following additional requirements apply to AFP testing of amniotic fluid specimens:

(i) The laboratory must validate its amniotic fluid method for AFP by assaying at least 100 amniotic fluid specimens at each gestational week between the 15th and 22nd week for which it can be confirmed that a normal fetus was delivered. While normal values are being determined, a laboratory may use normal values specified in the manufacturer's package insert. An elevated level must be confirmed, however, with repeat testing by a laboratory which has established its own normal values. Median values for each gestational week are established based upon these assays.

(ii) The standardization procedure, quality control, and reporting requirements for serum and plasma specimens also are required when testing amniotic fluid specimens.

(4) The following requirements apply for reporting the results of AFP testing:

(i) Test results will be released by the laboratory only if the laboratory is in possession of information required in §§ 74.22 (d)(1)(i), (v), (vi), (vii), (ix), (x), and (xi). If the laboratory is not in possession of items (ii), (iii), (iv), and (viii), the laboratory will release the test results only if the physican, coordinator, or laboratory determines that the lack of such information does not jeopardize the identification of that patient or the interpretation of the test results for that patient. In addition to the requirements for reporting at § 74.54, all positive screening test results must be communicated promptly to the attending physician and to the coordinator as defined in 21 CFR Part 899, Subpart E, by telephone or other rapid system. Written confirmation of results will be transmitted to the physician as soon as possible.

(ii) The report (phoned and written) shall include the patient's name, type of specimen, numerical value of the test result as a multiple of the normal median value at the same gestational week, and the equivalent mass or international units. In addition, the report must include a statement in the same terms of the laboratory's cutoff values above which a result is considered abnormal.

PART 405—FEDERAL HEALTH INSURANCE FOR THE AGED AND DISABLED

It is propsoed to amend 42 CFR Part 405 as follows: § 405.1317(b) is amended by adding a new subparagraph (9) reading as follows:

§ 405.1317 Condition—quality control.

* * * * *

(b) * * *

(9) Any laboratory performing screening or diagnostic tests to determine alpha-fetoprotein levels on serum or amniotic fluid obtained from pregnant patients shall meet the requirements specified in 42 CFR 74.22(d). These tests may be performed in serology or chemistry.

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